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THE IMPACT OF T-REGULATORY CELLS ON CANCER STEM CELLS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *One of the key challenges in modern oncology remains tumor resistance to therapy and the high risk of relapse, which are largely associated with cancer stem cells (CSCs). Regulatory T cells (Tregs) are considered one of the factors supporting the stem-like phenotype of tumor cells; however, the mechanisms of their interaction remain insufficiently studied. Despite the growing number of studies addressing the impact of Tregs on CSCs in breast cancer (BC), colorectal cancer (CRC), and glioblastoma (GBM), the fragmented and contradictory findings necessitated the con-duct of this analytical review.*

The study aimed to *systematize experimental, review, and clinical data on Treg-CSC interactions and to formulate hypotheses that define future research directions and therapeutic approaches.*

Methods: *This comprehensive literature search was conducted in Medline (PubMed), NCBI, and Google Scholar databases covering the years 2015 to 2025. The following terms were used: "T-regulatory cells" and/or "cancer stem cells" and/or "breast cancer stem cells" and/or "colorectal cancer stem cells" and/or "glioma stem cells."*

Results: *The literature review showed that Tregs, both directly and indirectly, activate key signaling cascades (TGF-β/SMAD, NF-κB/CCL1, IL-10/STAT3) that maintain the stem-like phenotype of tu-mor cells and are associated with poor prognosis in BC, CRC, and GBM.*

Conclusion: *Tregs and the molecular mechanisms they mediate can be considered potential targets for anticancer therapy; however, their use in clinical practice requires further experimental and clinical research.*

Keywords: *Regulatory T cells (Treg), cancer stem cells (CSCs), breast cancer stem cells, colorectal cancer stem cells, glioblastoma (GBM), oncological diseases, oncoimmunology.*

Introduction: According to GLOBOCAN data for 2022, malignant tumors are the cause of more than 9.7 million deaths, of which 9.3% were due to colorectal cancer (CRC), 6.8% to breast cancer (BC), and 2.6% to tumors of the central nervous system, including glioblastoma [1]. In the Republic of Kazakhstan in 2022, more than 20 thousand deaths from oncological diseases were registered, of which 9.5% were due to CRC, 7.6% to breast cancer, and 2.8% to tumors of the central nervous system, including glioblastoma (GBM) [2].

The high recurrence rate and resistance to cancer therapy are largely explained by the presence of cancer stem cells (CSCs). CSCs are a subpopulation of cancer cells that possess the ability to self-renew and undergo multilineage differentiation, which enables them to stimulate tumor development and heterogeneity [3]. CSCs can reduce the effectiveness of antitumor therapy by activating treatment-resistant molecular mechanisms [4].

Within the tumor microenvironment, CSCs interact with multiple immunosuppressive cell populations. These include tumor-associated macrophages, myeloid-derived suppressor cells, cancer-associated fibroblasts, and regulatory T cells (Treg). The latter are recruited to the tumor microenvironment by the chemokines CCR4, CCR8, and CCR10, as well as CXCR3 [5]. Tregs are capable not only of suppressing the antitumor immune response but, as many review articles have shown, also of directly or indirectly supporting the stem cell phenotype of tumor cells [6-12].

Published studies on this topic have yielded disparate results to date, with most reviews focusing on specific tumor types or specific molecular mechanisms. Therefore, this review aims to systematize and critically examine the data regarding the role of Tregs in regulating CSCs in breast cancer, CRC, and GBM.

The study aimed to systematize experimental, review, and clinical data on Treg-CSC interactions and to formulate hypotheses that define future research directions and therapeutic approaches.

Materials and Methods: To search for available literature data on the research topic, scientific publications from 2015 to 2025 indexed in the Medline (PubMed), NCBI, and Google Scholar databases were analyzed. The following terms were used in the search: "T-regulatory cells" AND/OR "cancer stem cells" AND/OR "breast cancer

stem cells" AND/OR "colorectal cancer stem cells" AND/OR "leukemic stem cell" AND/OR "glioma stem cells." The search revealed 89 potentially relevant sources (articles and reviews) on the research topic. After removing duplicates and assessing their content, the most significant and informative works (including reviews and descriptions of original research) were selected. The selection criteria were novelty, completeness of the data presented, and the presence of unique information (works of low quality or those duplicating data from previously published studies were excluded). The final analysis included 48 sources.

The source selection process included several sequential stages. At the identification stage, 89 publications were identified from the Medline (PubMed), NCBI, and Google Scholar databases. After removing 9 duplicate records, 80 sources were included in the analysis. At the abstract screening stage, 15 articles that did not mention Tregs were excluded. A total of 65 publications were selected for full-text evaluation, of which 17 were excluded due to insufficient data (n=4), lack of reliable results (n=5), overlap with previously published materials (n= 4), and failure to meet language criteria (n=4). Thus, the final systematic analysis included 48 articles that most fully and reliably reflect the molecular mechanisms of interaction between Tregs and CSCs in various malignant tumors. Inclusion criteria were: original studies or reviews, a clear description of the interaction between Tregs and CSCs, and the presence of data on signaling mechanisms or clinical correlations. Publications were selected independently by two authors. The source selection process is presented in the PRISMA diagram (Figure 1).

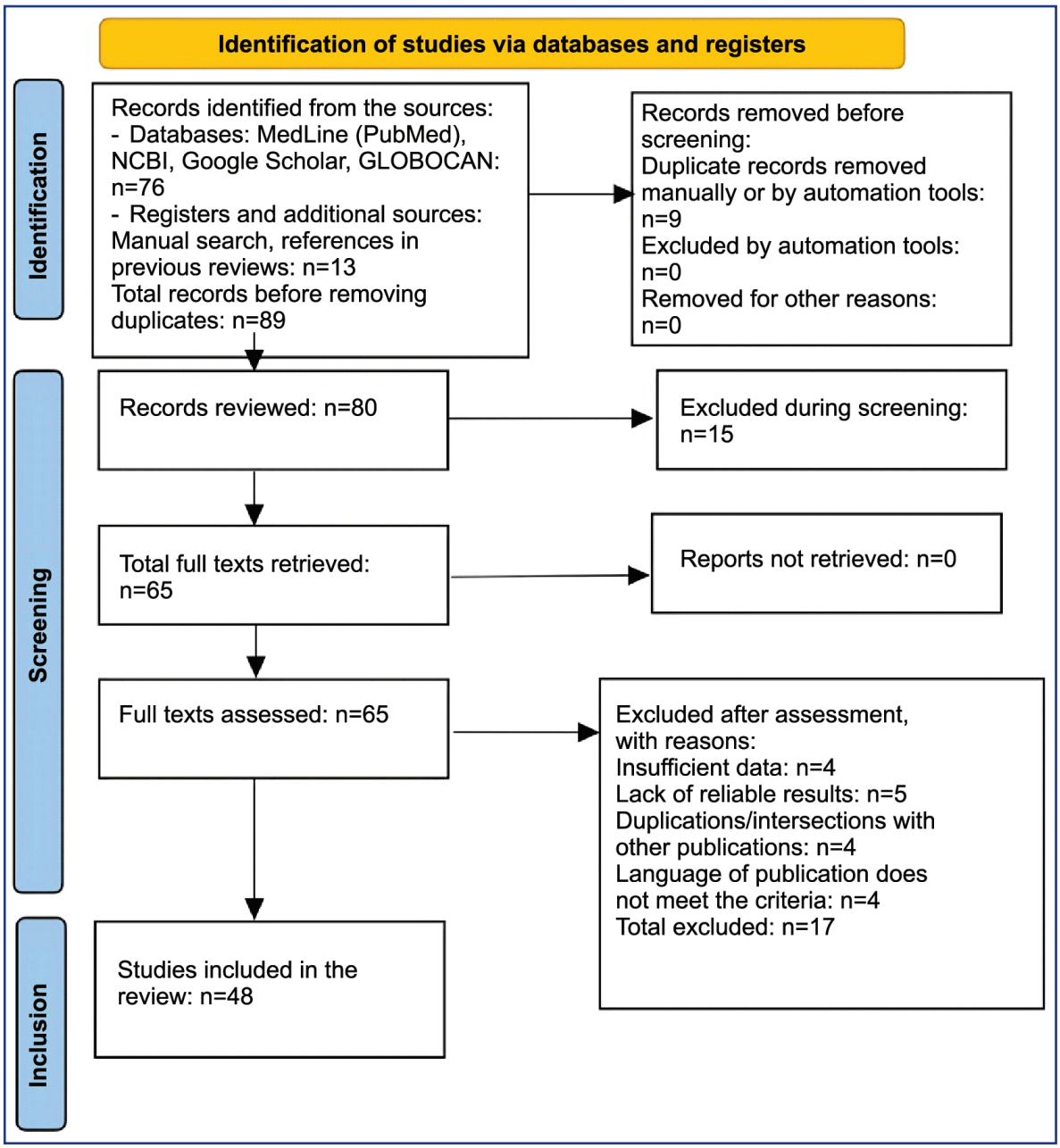


Figure 1 – PRISMA diagram reflecting the process of selecting sources for analysis

Results:

General characteristics of cancer stem cells. CSCs are a subpopulation of cancer cells that contribute to tumor development and heterogeneity. Seven common core intracellular signaling pathways are involved in both embryonic development and malignancy (Table 1).

Table 1 – Main intracellular signaling pathways of cancer stem cells (CSCs)

Signaling pathways	Key effects for CSCs	Source
JAK/STAT	Support of the stem cell phenotype promotes activa-tion of epithelial-mesenchymal transition (EMT), in-vasion, and metastasis	Huang B. et al. [13]
NOTCH	Regulation of differentiation, maintenance of the CSC population, and participation in drug resistance	Shi Q. et al. [14]
NF-κB	Activation of IL-6/IL-8 production, support of CSC survival, and development of drug resistance	Guo Q. et al. [15]
Wnt/β-catenin	Maintenance of self-renewal, activation of NANOG and c-MYC transcriptional programs, formation of therapeutic resistance	Song P. et al. [16]
TGF-β/SMAD	Initiation of EMP, enhancement of plasticity, and ex-pansion of the CSC pool	Allgayer H. et al. [17]
PI3K/AKT/mTOR	Metabolic adaptation of CSCs, maintenance of surviv-al, and resistance to therapy	Prabhu KS et al. [18]
MAPK/ERK	Stimulation of CSC proliferation and formation of tumor spheres	Chu X. et al. [19]

Even small numbers of isolated CSCs expressing characteristic stem cell markers can initiate tumor development in immunodeficient mice [20]. In some types of cancer, CSCs exhibit resistance to chemotherapeutic drugs such as docetaxel, doxorubicin, cyclophosphamide, and trastuzumab [21]. Therefore, this cell population is attracting increasing attention from researchers as a key target for the development of new cancer therapy strategies.

General characteristics of regulatory T cells. Tregs are a population of $CD4^+$ T-cells that regulate both innate and adaptive immune responses against the body's own cells, virulent agents, and tumors [22]. Tregs play a crucial role in maintaining immune system homeostasis by eliminating autoreactive T cells, promoting self-tolerance, and suppressing inflammatory processes [23].

FOXP3 is a specific marker of Tregs, which belongs to the family of regulatory transcription factors. In the absence of this protein expression, Tregs lose their ability to suppress the immune system [24].

The influence of regulatory T cells on breast cancer cancer stem cells. Breast cancer CSCs can differentiate into various tumor cell types, thereby maintaining tumor heterogeneity. Due to their self-renewal capacity, they provide a constant stem cell pool throughout breast cancer progression [25].

The NF-κB/CCL1 signaling cascade is a key molecular mechanism that recruits Tregs to tumor sites. Activation of the NF-κB transcription factor in CSCs leads to increased production of the chemokine CCL1, which promotes the recruitment of Tregs to the tumor microenvironment. Possessing pronounced immunosuppressive properties, Tregs not only suppress the antitumor response but also stimulate CSCs. They promote the increased expression of key stemness transcription factors—SOX2, OCT4, and NANOG [26–29].

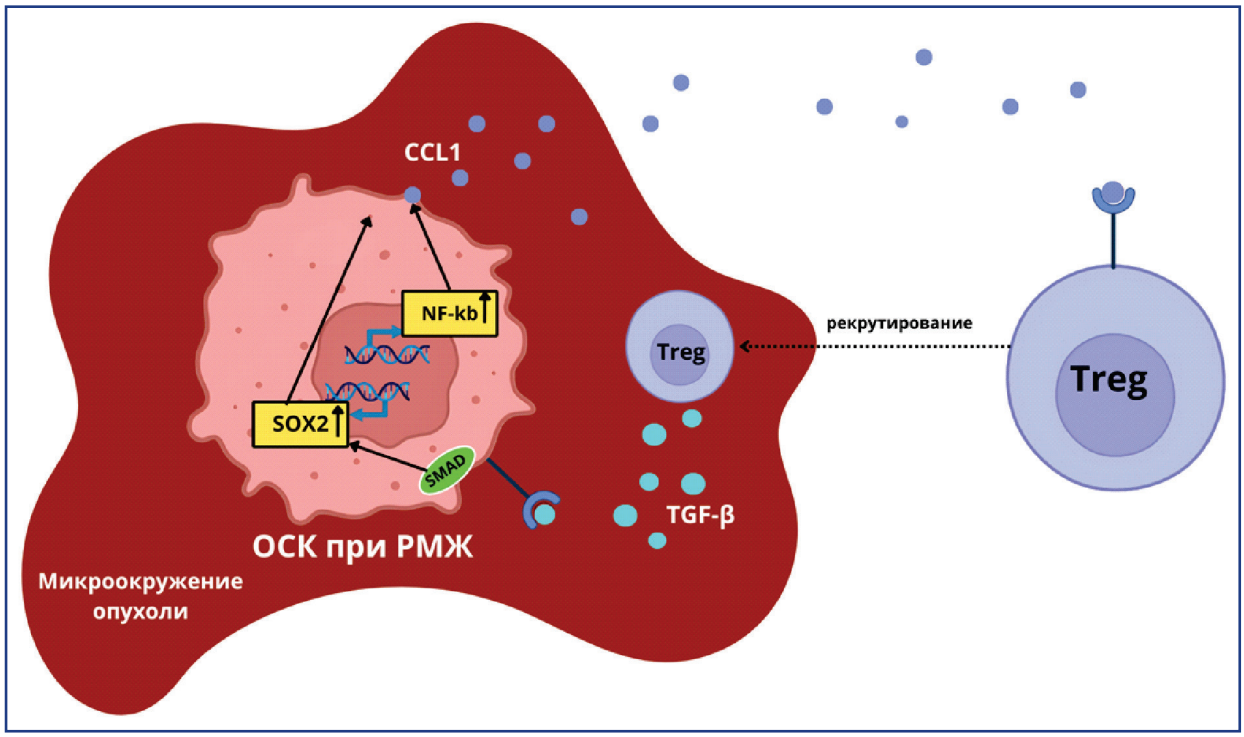
Interestingly, overexpression of SOX2 activates transcription of the chemokine CCL1, which, as previously reported, attracts Tregs to tumors [27]. Thus, a unique relationship emerges in which stem cell factor markers enhance tumor infiltration of Tregs, which in turn maintain a persistent CSC phenotype in breast cancer (Figure 2).

One of the primary mechanisms by which Tregs influence CSCs in breast cancer is the production of the cytokine TGF-β, which induces the expression of the aforementioned stem cell transcription factors, as well as the WNT3a and ESR1 *genes*. These genes, in turn, promote the formation of mammospheres – spherical structures consisting of a cluster of cells with stem cell properties [26, 28].

The influence of regulatory T cells on colorectal cancer cancer stem cells (CRC CSCs). One of the variants of direct interaction between CRC CSCs and Tregs is the RANKL/RANK molecular mechanism. The RANK receptor (TNFRSF11a), expressed on CRC CSCs, induces an increase in intracellular Ca^{2+} levels through the PLCγ-IP3-STIM1 signaling pathway. This leads to the dephosphorylation of NFATC1, which activates the transcription of the ACP5 gene, associated with an unfavorable prognosis in patients with cancer, particularly in those with CRC [30, 31].

Tregs, in turn, express RANKL (TNFRSF11), a ligand of the RANK receptor. It has been established that activation of the RANKL/RANK pathway leads to increased expression of CD44 and CD133, the main markers of CRC cells [32].

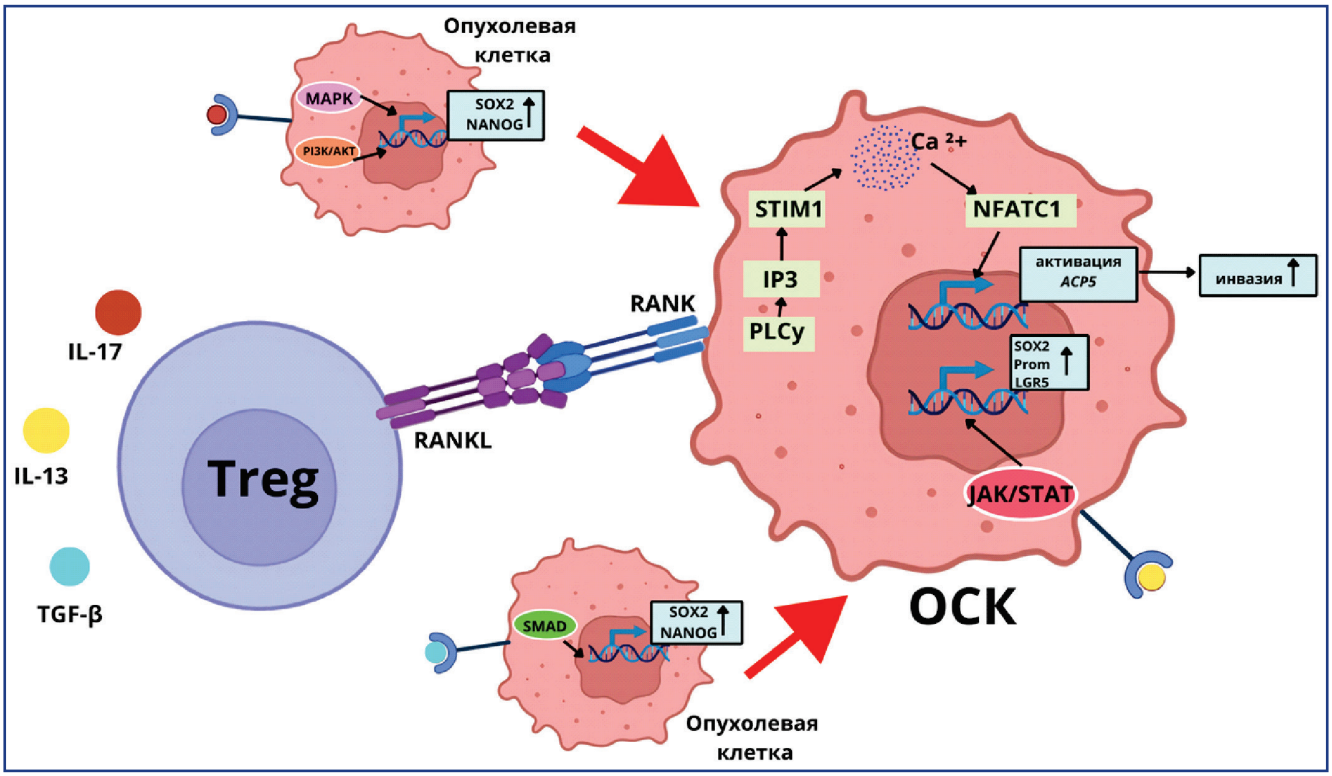
Cytokines such as TGF-β, IL-13, and IL-17 play a key role in stimulating the activity of CRC CSCs. TGF-β triggers epithelial-mesenchymal transition (EMT), thereby promoting the dedifferentiation of CRC cells into CRC CSCs. This leads to an expansion of the CRC CSCs' pool and increases tumor resistance to therapy [33, 34]. IL-13 activates the STAT3 signaling pathway, increasing the expression of *SOX2, LGR5, and Prom*1 genes, which are critical for tumor cell self-renewal and stemness maintenance [35, 36]. IL-17, through the activation of MAPK and AKT kinases, promotes the formation of CRC CSCs. It was also previously noted that IL-17 stimulates the expression of CD44, CD133, and CD166, which are markers of CRC cells [37] (Figure 3).



Legend: Микроокружение опухоли – Tumor microenvironment; ОСК при РМЖ – breast cancer CSCs; рекрутирование – recruiting

Figure 2 – The SOX2–CCL1–Treg loop supporting the CSC stemness in breast cancer

Note: The image was created by the author using the BioRender.com web resource.

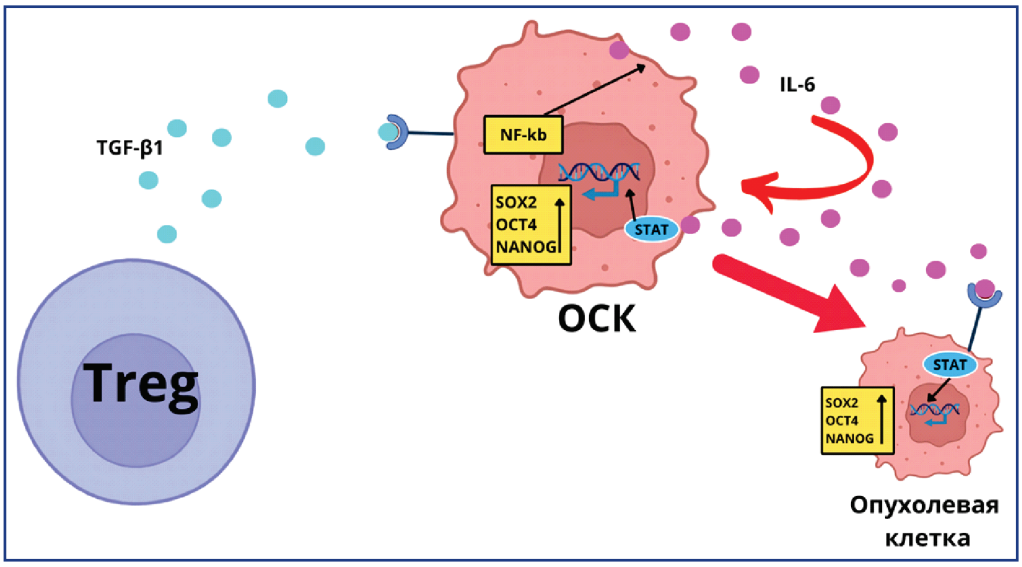


Legend: Опухолевая клетка – Cancer cell; Активация ACPS – ACPS activation; Инвазия – Invasion; ОСК – CSC

Figure 3 – Key molecular mechanisms of interaction between Tregs and colorectal cancer cells

Note: The image was created by the author using the BioRender.com web resource.

The influence of regulatory T cells on cancer stem cells in glioblastoma. One of the key mechanisms by which Tregs mediate their action on CSCs in glioblastoma is the secretion of TGF-β1, which stimulates the production of IL-6 by tumor cells. This cytokine activates the STAT signaling pathway in both autocrine and paracrine manners, inducing the expression of SOX2, OCT4, and NANOG (Figure 4). This leads to increased formation of neurospheres – spherical structures consisting of stem-like glioma cells that are associated with tumor aggressiveness [38].



Legend: Опухолевая клетка – Cancer cell; ОСК – CSC

Figure 4 – Indirect influence of Tregs on cancer stem cells in glioblastoma

Note: The image was created by the author using the BioRender.com web resource.

Discussion: The experimental preclinical studies and review articles reviewed above indicate the ability of Tregs to enhance the stem-like properties of tumor cells. Systematization of the available modern data enabled us to identify the best-studied molecular mechanisms by which Tregs influence CSCs in breast cancer, CRC, and GBM. The data presented in Table 2 demonstrate the similarity of the final effects of Tregs in the tumor types considered, despite the differences in their mechanisms of action. Tregs increase the activity of genes and transcription factors responsible for the stem-like properties of tumor cells, which ensures their survival, promotes the maintenance of CSC populations, and is associated with an unfavorable prognosis.

It is also worth noting that a common trend for all cancer types described in the article is the presence of a clinical correlation between a high level of Treg infiltration and unfavorable clinical outcomes, which is expressed in a reduction in overall survival (OS) and increased hazard ratio (HR) values for breast cancer, GBM, and CRC (Table 3).

Clinical cohort studies that simultaneously analyze CSCs and Tregs are currently limited in number. The most methodologically comprehensive example remains the study by TJ Miller et al., which found that Tregs modified the prognostic value of SOX2 in CRC [39]; however, comparable data are lacking for breast cancer and GBM. This highlights an unmet clinical need and provides direction for future research.

Based on the analysis of the presented material, we propose several hypotheses that could potentially form the basis for the development of new therapeutic strategies (Table 4).

However, the degree of clinical feasibility of these hypotheses varies. Thus, cytokine blockade has been preclinically confirmed [38, 47-48], while simultaneous blockade of Treg chemokine receptors and key CSC signaling pathways requires further experimental and clinical studies.

This review has several limitations that must be considered when interpreting the results. Most of the studies reviewed were conducted in preclinical settings (cell lines, animal models), which limits their direct extrapolation to clinical practice. The differences between individual Treg subtypes (FoxP3E2+, CCR8+, CD177+) and their impact on the CSC population were not examined in detail, leaving unclear which Treg subsets play a key role in maintaining the stem cell phenotype. The question of how modern therapies (immunotherapy, chemotherapy, targeted therapy) modify the balance between Treg and CSCs is also insufficiently addressed. Furthermore, the temporal aspects of Treg recruitment to tumors, the specifics of their direct contacts with CSCs in vivo, and the consequences of therapeutic Treg modification for tumor resistance and the effectiveness of immunotherapy remain poorly understood.

At the same time, this review is not limited to listing individual molecular mechanisms, but represents an attempt to synthesize disparate data into a holistic model of the role of Tregs in maintaining CSCs. It has been demonstrated that Tregs are involved not only in the formation of an immunosuppressive microenvironment but also directly support the stem phenotype through the activation of signaling pathways, such as TGF-β/SMAD, IL-10/STAT3, NF-κB/CCL1, and RANKL/RANK. These mechanisms are associated with the induction of transcription factors SOX2, OCT4, and NANOG, as well as increased expression of stemness markers (CD44, CD133), and are linked to the formation of mammospheres and neurospheres, which reflects the plasticity and therapeutic resistance of tumors.

The contribution of this review lies not only in its systematization of existing data but also in the formulation of its own hypotheses. The proposed approaches, based on a comparison of current data, allow us to identify specific directions for further preclinical and clinical validation.

Table 2 – Clinical data on the association of Treg infiltration with hazard ratio for overall survival in patients with breast cancer, colorectal cancer, and glioblastoma

Tumor type	Key mechanisms of Treg influence on CSCs		The involved CSC signaling pathway	Impact on SCS	Clinical significance	Sources
	Indirect	Direct				
Breast cancer	TGF-β (via activation of EMP)	-	TGF-β/SMAD	1. Increased expression of SOX2, OCT4 and NANOG. 2. Increased expression of *WNT3a* and *ESRG* genes, and an accordingly higher number of mammospheres.	It is associated with a severe clinical course: early relapses, metastasis, and poor prognosis.	[26, 27, 39]
Colorectal cancer	-	RANKL/RANK (via the PLCy-IP3-STIM1 signaling pathway)	Cross-activation of signaling pathways: Wnt/β-catenin NF – κB PI3K/AKT JAK/STAT	1. Activates transcription of the ACP5 gene 2. Enhance the expression of stemness markers CD44 and CD133.	Increased tumor size and metastasis; decreased overall and relapse-free patient survival.	[30-32]
	TGF-β (via EMF)	-	TGF-β/SMAD	Dedifferentiation of CRC cells into CRC CSCs.	Increased recurrence rate; Decreased overall survival; Reduced sensitivity to chemotherapy; High risk of metastatic spread	[33-37, 42, 43]
	IL-13 (via STAT3)	-	JAK/STAT	Increased expression of *SOX2, LGR5 genes*		
	IL-17	-	MAPK/ERK PI3K/AKT	Stimulation of expression of stemness markers CD44, CD133, and CD166.		
Glioblastoma	TGF-β1 (via stimulation of IL-6 production)	-	NF-κB JAK/STAT	1. Induction of expression of stem transcription factors: SOX2, OCT4, and NANOG. 2. Formation of neurospheres	Associated with tumor aggressiveness, as well as poor prognosis and resistance to therapy	[38, 41]

Table 3 – Clinical data on the association of Treg infiltration with hazard ratio to overall survival in patients with breast cancer, colorectal cancer, and glioblastoma

Tumor type	Study design	Cohort, n	Hazard ratio for overall survival	p-value	Confidence interval	Prognosis	Source
Breast cancer	Cohort study	990	1.8	p = 0.014	1.1-2.8	Adverse	[28]
Breast cancer	Meta-analysis	8666	1.60	p < 0.05	1.06-2.42	Adverse	[44]
Colorectal cancer	Retrospective cohort study	1720	1.35	p = 0.028	–	Adverse	[45]
Glioblasto-ma	Bioinformatic analysis	152	1.199	p < 0.001	1.101-1.305	Adverse	[46]

Table 4 Potential strategies for blocking Treg-mediated mechanisms and their impact on cancer stem cells (CSCs)

Гипотеза	Потенциальный механизм действия	Предполагаемый эффект
Simultaneous block-ade of Treg chemo-kine receptors (CCR4, CCR8) and key CSC signaling pathways in breast cancer	Blocking Treg chemokine receptors (CCR4, CCR8) with monoclonal antibodies can limit the re-cruitment and migration of Tregs into the tumor microenvironment. Suppression of key intracellular signaling pathways using small-molecule inhibitors or epigenetic inhibitors.	1. A decrease in the number of Tregs in the tumor microenvironment could potentially partially reduce immunosuppression, contributing to the normalization of the antitumor activity of $CD8^+$ T-cells. 2. Suppression of key CSC signaling pathways will reduce the expression of the CSC stem cell phenotype, re-sistance to therapy, and the likelihood of relapse.
Blockade of IL-6 cy-tokines in glioblas-toma	Inhibition of IL-6 prevents the activation of the JAK/STAT pathway, which in turn blocks the expression of SOX2, OCT4, and NANOG.	1. Reduced autocrine and paracrine support of CSC stem cell phenotype. 2. Reduced neurosphere formation associated with maintenance of CSC population. 3. Reduced CSC pool will weaken their ability to self-renew and recover after therapy.
TGF-β cytokine blockade for breast cancer, glioblastoma, and colorectal cancer	Neutralization of TGF-β pre-vents SMAD-dependent acti-vation of EMT.	1. Limited activation of stem transcription factors (SOX2, OCT4, NANOG). 2. Decreased formation of mammospheres and neurospheres. 3. Reduced CSC tumor cell dedifferentiation. 4. Reduced CSC pool.

Conclusion: The combined data presented indicate that Tregs may be involved not only in forming an immunosuppressive microenvironment but also in maintaining the properties of CSCs that determine the aggressiveness of the disease and resistance to therapy. Although this relationship has not yet been definitively confirmed clinically, a comparison of experimental and clinical observations suggests it as a promising avenue for further research.

References:

1. GLOBOCAN. World Fact Sheet. – 2022. – Accessed on: 19.09.2025. – URL: https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf

2. GLOBOCAN. Kazakhstan Fact Sheet. – 2022. – Accessed on: 19.09.2025. – URL: https://gco.iarc.who.int/media/globocan/factsheets/populations/398-kazakhstan-fact-sheet.pdf

3. Ayob A.Z., Ramasamy T.S. Cancer stem cells as key drivers of tumour progression // J.Biomed. Sci. – 2018. – Vol. 25. – Art. no. 20. https://doi.org/10.1186/s12929-018-0426-4

4. Phi L.T.H., Sari I.N., Yang Y.G., Lee S.H., Jun N., Kim K.S., Lee Y.K., Kwon H.Y. Cancer Stem Cells (CSCs) in Drug Resistance and their Therapeutic Implications in Cancer Treatment // Stem Cells Int. – 2018. – Art. no. 5416923. https://doi.org/10.1155/2018/5416923

5. Abdul-Rahman T., Ghosh S., Badar S.M. The paradoxical role of cytokines and chemokines at the tumor microenvironment: a comprehensive review // Eur. J. Med. Res. – 2024. – Vol. 29. – Art. no. 124. https://doi.org/10.1186/s40001-024-01711-z

6. Yousefnia S., Seyed Forootan F., Seyed Forootan S., Nasr Esfahani M.H., Gure A.O., Ghaedi K. Mechanistic pathways of malignancy in breast cancer stem cells // Front. Oncol. – 2020. – Vol. 10. – Art. no. 452. https://doi.org/10.3389/fonc.2020.00452

7. Tsui Y.M., Chan L.K., Ng I.O. Cancer stemness in hepatocellular carcinoma: mechanisms and translational potential // Br. J. Cancer. – 2020. – Vol. 122. – P. 1428–1440. https://doi.org/10.1038/s41416-020-0823-9

8. Oshimori N., Oristian D., Fuchs E. TGF-β promotes heterogeneity and drug resistance in squamous cell carcinoma // Cell – 2015. – Vol. 160, No. 5. – P. 963–976. https://doi.org/10.1016/j.cell.2015.01.043

9. Kim B.N., Ahn D.H., Kang N. TGF-β induced EMT and stemness characteristics are associated with epigenetic regulation in lung cancer // Sci. Rep. – 2020. – Vol. 10. – Art. no. 10597. https://doi.org/10.1038/s41598-020-67325-7

10. Xu Y., Mou J., Wang Y., Zhou W., Rao Q., Xing H. Regulatory T cells promote the stemness of leukemia stem cells through IL10 cytokine-related signaling pathway // Leukemia. – 2022. – Vol. 36(2). – P. 403–415. https://doi.org/10.1038/s41375-021-01375-2

11. Wei S., Li J., Tang M., Zhang K., Gao X., Fang L., Liu W. STAT3 and p63 in the Regulation of Cancer Stemness // Front. Genet. – 2022. – Vol. 13. – Art. no. 909251. https://doi.org/10.3389/fgene.2022.909251

12. Lei M.M.L., Lee T.K.W. Cancer stem cells: Emerging key players in immune evasion of cancers // Front. Cell Dev. Biol. – 2021. – Vol. 9. – Art. no. 692940. https://doi.org/10.3389/fcell.2021.692940

13. Huang B., Lang X., Li X. The role of IL-6/JAK2/STAT3 signaling pathway in cancers // Front. Oncol. – 2022. – Vol. 12. – Art. no. 1023177. https://doi.org/10.3389/fonc.2022.1023177

14. Shi Q., Xue C., Zeng Y., Yuan X., Chu Q., Jiang Sh., Wang J., Zhang Y., Zhu D., Li L. Notch signaling pathway in cancer: from mechanistic insights to targeted therapies // Sig. Transduct. Target Ther. – 2024. – Vol. 9. – Art. no. 128. https://doi.org/10.1038/s41392-024-01828-x

15. Guo Q., Jin Y., Chen X., Ye X., Shen X., Lin M., Zeng Ch., Zhou T., Zhang J. NF-κB in biology and targeted therapy: new insights and translational implications // Sig. Transduct. Target Ther. – 2024. – Vol. 9. – Art. no. 53. https://doi.org/10.1038/s41392-024-01757-9

16. Song P., Gao Z., Bao Y., Chen L., Huang Y., Liu Y., Dong Q., Wei X. Wnt/β-catenin signaling pathway in carcinogenesis and cancer therapy // J. Hematol. Oncol. – 2024. – Vol. 17(1). – Art. no. 46. https://doi.org/10.1186/s13045-024-01563-4

17. Allgayer H., Mahapatra S., Mishra B., Swain B., Saha S., Khanra S., Kumari K., Panda V.K., Malhotra D., Patil N.S., Leupold J.H., Kundu G.C. Epithelial-to-mesenchymal transition (EMT) and cancer metastasis: the status quo of methods and experimental models 2025 // Mol. Cancer. – 2025. – Vol. 24. – P. 167. https://doi.org/10.1186/s12943-025-02338-2

18. Prabhu K.S., Kuttikrishnan S., Mariyam Z., Habeeba U., Panicker A.J., Masoodi T., Junejo K., Uddin S. PI3 K/AKT/mTOR pathway and its role in breast cancer stem cells //Naunyn-Schmiedeberg's Arch Pharmacol. – 2025. – Online ahead of print. https://doi.org/10.1007/s00210-025-04297-3

19. Chu X., Tian W., Ning J., Xiao G., Zhou Y., Wang Z., Zhai Z., Tanzhu G., Yang J., Zhou R. Cancer stem cells: advances in knowledge and implications for cancer therapy // Sig. Transduct. Target Ther. – 2024. – Vol. 9. – Art. no. 170. https://doi.org/10.1038/s41392-024-01851-y

20. Kim W., Ryu C.J. Cancer stem cell surface markers on normal stem cells // BMB Rep. – 2017. – Vol. 50. – P. 285-298. https://doi.org/10.5483/BMBRep.2017.50.6.039

21. Zheng Q., Zhang M., Zhou F., Zhang L., Meng X. The Breast Cancer Stem Cells Traits and Drug Resistance // Front. Pharmacol. – 2021. – Vol. 11. – Art. no. 599965. https://doi.org/10.3389/fphar.2020.599965

22. Okeke E.B., Uzonna J.E. The Pivotal Role of Regulatory T Cells in the Regulation of Innate Immune Cells // Front. Immunol. – 2019. – Vol. 10. – P. 680. https://doi.org/10.3389/fimmu.2019.00680

23. Grover P., Goel P.N., Greene M.I. Regulatory T Cells: Regulation of Identity and Function // Front. Immunol. – 2021. – Vol. 12 – Art. no. 750542. https://doi.org/10.3389/fimmu.2021.750542

24. Attias M., Al-Aubodah T., Piccirillo C.A. Mechanisms of human FoxP3+ Treg cell development and function in health and disease //

Clin. Exp. Immunol. – 2019. – Vol. 197, No. 1. – P. 36-51. https://doi.org/10.1111/cei.13290

25. Zhang L., Chen W., Liu S., Chen C. Targeting Breast Cancer Stem Cells // Int. J. Biol. Sci. – 2023. – Vol. 19, No. 2. – P. 552–570. https://doi.org/10.7150/ijbs.76187

26. Xu Y., Dong X., Qi P., Ye Y., Shen W., Leng L., Wang L., Li X., Luo X., Chen Y., Sun P., Xiang R., Li N. Sox2 Communicates with Tregs Through CCL1 to Promote the Stemness Property of Breast Cancer Cells // Stem Cells. – 2017. – Vol. 35(12). – P. 2351–2365. https://doi.org/10.1002/stem.2720

27. Mehraj, U., Ganai, R. A., Macha, M. A., Hamid, A., Zargar, M. A., Bhat, A. A., Nasser, M. W., Haris, M., Batra, S. K., Alshehri, B., Al-Baradie, R. S., Mir, M. A., & Wani, N. A. (2021). The tumor microenvironment as driver of stemness and therapeutic resistance in breast cancer: New challenges and therapeutic opportunities. Cellular oncology (Dordrecht, Netherlands), 44(6), 1209–1229. https://doi.org/10.1007/s13402-021-00634-9

28. Fusco C., Di Rella F., Liotti A., Colamatteo A., Ferrara A.L., Gigantino V., Collina F., Esposito E., Donzelli I., Porcellini A., Feola A., Micillo T., Perna F., Garziano F., Maniscalco G.T., Varricchi G., Mottola M., Zuccarelli B., De Simone B., di Bonito M., … De Rosa V. CD4+FOXP3Exon2+ regulatory T cell frequency predicts breast cancer prognosis and survival // Sci. Adv. – 2025. – Vol. 11. – Art. no. eadr7934. https://doi.org/10.1126/sciadv.adr7934

29. Guha A., Goswami K., Sultana J., Ganguly N., Choudhury P., Chakravarti M., Bhuniya A., Sarkar A., Bera S., Dhar S., Das J., Das D., Baral R., Bose A., Banerjee S. Cancer stem cell–immune cell crosstalk in breast tumor microenvironment: a determinant of therapeutic facet // Front. Immunol. – 2023. – Vol. 14. – Art. no. 1245421. https://doi.org/10.3389/fimmu.2023.1245421

30. Liang Q., Wang Y., Lu Y. RANK promotes colorectal cancer migration and invasion by activating the Ca2+-calcineurin/NFATC1-ACP5 axis // Cell Death Dis. – 2021. – Vol. 12. – Art. no. 336. https://doi.org/10.1038/s41419-021-03642-7

31. Bian Z.Q., Luo Y., Guo F., Huang Y.Z., Zhong M., Cao H. Overexpressed ACP5 has prognostic value in colorectal cancer and promotes cell proliferation and tumorigenesis via FAK/PI3K/AKT signaling pathway // Am. J. Cancer Res. – 2019. – Vol. 9, No. 1. – P. 22–35. https://pmc.ncbi.nlm.nih.gov/articles/PMC6356923/

32. Ouyang J., Hu S., Zhu Q. RANKL/RANK signaling recruits Tregs via the CCL20–CCR6 pathway and promotes stemness and metastasis in colorectal cancer // Cell Death Dis. – 2024. – Vol. 15. – P. 437. https://doi.org/10.1038/s41419-024-06806-3

33. Nakano M., Kikushige Y., Miyawaki K. Dedifferentiation process driven by TGF-β signaling enhances stem cell properties in human colorectal cancer // Oncogene – 2019. – Vol. 38. – P. 780-793. https://doi.org/10.1038/s41388-018-0480-0

34. Hao Y., Baker D., Ten Dijke P. TGF-β-mediated epithelial-mesenchymal transition and cancer metastasis // Int. J. Mol. Sci. – 2019. – Vol. 20(11). – Art. no. 2767. https://doi.org/10.3390/ijms20112767

35. Zhao R., Cao G., Zhang B. TNF+ regulatory T cells regulate the stemness of gastric cancer cells through the IL13/STAT3 pathway // Front. Oncol. – 2023. – Vol. 13. – Art. no. 1162938. https://doi.org/10.3389/fonc.2023.1162938

36. He B., Liang J., Qin Q., Zhang Y., Shi S., Cao J., Zhang Z., Bie Q., Zhao R., Wei L., Zhang B. IL-13/IL-13RA2 Signaling Promotes Colorectal Cancer Stem Cell Tumorigenesis by Inducing Ubiquitinated Degradation of p53 // Genes Dis. – 2024. – Vol. 11, No. 1. – P. 495–508. https://doi.org/10.1016/j.gendis.2023.01.027

37. Becerril-Rico J., Alvarado-Ortiz E., Toledo-Guzmán M.E., Pelayo R., Ortiz-Sánchez E. The cross talk between gastric cancer stem cells and the immune microenvironment: a tumor-promoting factor // Stem Cell Res. Ther. – 2021. – Vol. 12(1). – P. 498. https://doi.org/10.1186/s13287-021-02562-9

38. Liu S., Zhang C., Wang B., Zhang H., Qin G., Li C., Cao L., Gao Q., Ping Y., Zhang K., Lian J., Zhao Q., Wang D., Zhang Z., Zhao X., Yang L., Huang L., Yang B., Zhang Y. Regulatory T cells promote glioma cell stemness through TGF-β–NF-κB–IL6–STAT3 signaling // Cancer Immunol. Immunother. – 2021. – Vol. 70. – P. 2601-2616. https://doi.org/10.1007/s00262-021-02872-0

39. Miller T.J., McCoy M.J., Hemmings C., Bulsara M.K., Iacopetta B., Platell C.F. The prognostic value of cancer stem-like cell markers SOX2 and CD133 in stage III colon cancer is modified by expression of the immune-related markers FoxP3, PD-L1 and CD3 // Pathology. – 2017. – Vol. 49(7). – P. 721-730. https://doi.org/10.1016/j.pathol.2017.08.007

40. Ji P., Zhang Y., Wang S., Ge H., Zhao G., Xu Y., Wang Y. CD44hiCD24lo mammosphere-forming cells from primary breast cancer display resistance to multiple chemotherapeutic drugs // Oncol. Rep. – 2016. – Vol. 35(6). – P. 3293-3302. https://doi.org/10.3892/or.2016.4739

41. Bradshaw A., Wickremsekera A., Tan S.T., Peng L., Davis P.F., Itinteang T. Cancer stem cell hierarchy in glioblastoma multiforme // Front. Surg. – 2016. – Vol. 3. – P. 21. https://doi.org/10.3389/fsurg.2016.00021

42. Takeda K., Mizushima T., Yokoyama Y. Sox2 is associated with cancer stem-like properties in colorectal cancer // Sci. Rep. – 2018. – Vol. 8. – Art. no. 17639. https://doi.org/10.1038/s41598-018-36251-0

43. Han S., Yang W., Zong S., Li H., Liu S., Li W., Shi Q., Hou F. Clinicopathological, prognostic and predictive value of CD166 expression in colorectal cancer: a meta-analysis // Oncotarget. – 2017. – Vol. 8(38). – P. 64373-64384. https://doi.org/10.18632/oncotarget.17442

44. Shou J., Zhang Z., Lai Y., Chen Z., Huang J. Worse outcome in breast cancer with higher tumor-infiltrating FOXP3+ Tregs: a systematic review and meta-analysis // BMC Cancer. – 2016. – Vol. 16(1). – P. 687. https://doi.org/10.1186/s12885-016-2732-0

45. Bergsland C.H., Jeanmougin M., Moosavi S.H., Svindland A., Bruun J., Nesbakken A., Sveen A., Lothe R.A. Spatial analysis and CD25-expression identify regulatory T cells as predictors of a poor prognosis in colorectal cancer // Mod. Pathol. – 2022. – Vol. 35. – P. 1236-1246. https://doi.org/10.1038/s41379-022-01086-8

46. Guo X, Zhang G, Wang Z, Duan H, Xie T, Liang L, Cui R, Hu H, Wu Y, Dong J, He Z, Mou Y. A novel Foxp3-related immune prognostic signature for glioblastoma multiforme based on immunogenomic profiling // Aging (Albany NY). – 2021. – Vol. 13. – P. 3501-3517. https://doi.org/10.18632/aging.202282

47. Chung A., Kozielski A., Qian W., Zhou J., Anselme A., Chan A., Pan P.-Y., Lee D., Chang J. Tocilizumab overcomes chemotherapy resistance in mesenchymal stem-like breast cancer by negating autocrine IL-1A induction of IL-6 // NPJ Breast Cancer. – 2022. – Vol. 8. – Art. no. 30. https://doi.org/10.1038/s41523-021-00371-0

48. Futakuchi M., Lami K., Tachibana Y., Yamamoto Y., Furukawa M., Fukuoka J. The effects of TGF-β signaling on cancer cells and cancer stem cells in the bone microenvironment // Int. J. Mol. Sci. – 2019. – Vol. 20(20). – Art. no. 5117. https://doi.org/10.3390/ijms20205117

АҢДАТПА

Т-РЕГУЛЯТОРЛЫҚ ЖАСУШАЛАРДЫҢ ҚАТЕРЛІ ІСІК ДІҢ ЖАСУШАЛАРЫНА ТИГІЗЕТІН ЫҚПАЛЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Қазіргі онкологияның негізгі мәселелерінің бірі – ісіктердің терапияға төзімділігі және қайталану қаупінің жоғары болуы, бұл көбінесе ісік бағаналы жасушаларымен (ІБЖ) байланысты. Регуляторлы Т-жасушалар (Treg) ісік жасушаларының бағаналы фенотипін қолдайтын факторлардың бірі ретінде қарастырылады, алайда олардың өзара әрекеттесу механизмдері жеткілікті зерттелмеген. Сүт безі обыры (СБО), колоректалды обыр (КРО) және глиобластома*

(ГБМ) кезіндегі Treg пен ІБЖ әсеріне арналған зерттеулер санының артуына қарамастан, нәтижелер әлі де фрагментті және қарама-қайшы болып отыр. Бұл аналитикалық шолуды жүргізудің қажеттілігін айқындайды.

***Зерттеу мақсаты** – Treg пен ІБЖ өзара әрекеттесуіне қатысты эксперименттік, шолу және клиникалық деректерді жүйелеу және келешектегі зерттеулер мен терапевтік тәсілдерді айқындайтын гипотезаларды тұжырымдау.*

***Әдістері:** Medline (PubMed), NCBI, Google Scholar деректер базаларында 2015 жылдан 2025 жылға дейін кешенді әдебиет іздеуі жүргізілді. Іздеу кезінде мына терминдер қолданылды: «T-regulatory cells» және/немесе «cancer stem cells» және/немесе «breast cancer stem cells» және/немесе «colorectal cancer stem cells» және/немесе «glioma stem cells».*

***Нәтижелері:** Әдеби шолу Treg жасушаларының тікелей де, жанама түрде де негізгі сигналдық каскадтарды (TGF-β/SMAD, NF-κB/CCL1, IL-10/STAT3) белсендіріп, ісік жасушаларының бағаналы фенотипін қолдайтынын және олардың СБО, КРО және ГБМ кезінде қолайсыз болжаммен байланысты екенін көрсетті.*

***Қорытынды:** Treg және олардың опосредиялайтын молекулалық механизмдері ісікке қарсы терапия үшін әлеуетті нысан ретінде қарастырылуы мүмкін, алайда клиникалық практикаға енгізу үшін қосымша эксперименттік және клиникалық зерттеулер қажет.*

***Түйінді сөздер:** Регуляторлы Т-жасушалар (Treg), ісік бағаналы жасушалары, сүт безі обырының бағаналы жасушалары, колоректалды обырдың бағаналы жасушалары, глиобластома, онкологиялық аурулар, онкоиммунология.*

АННОТАЦИЯ

ВЛИЯНИЕ РЕГУЛЯТОРНЫХ Т-КЛЕТОК НА ОПУХОЛЕВЫЕ СТВОЛОВЫЕ КЛЕТКИ: ОБЗОР ЛИТЕРАТУРЫ

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***Актуальность:** Одной из ключевых проблем современной онкологии остаётся устойчивость опухолей к терапии и высокий риск рецидивов, во многом связанных с опухолевыми стволовыми клетками (ОСК). Регуляторные Т-клетки (Treg) рассматриваются как один из факторов, поддерживающих стволовой фенотип опухолевых клеток, однако механизмы их взаимодействия остаются недостаточно изученными. Несмотря на возрастающее число исследований, посвящённых влиянию Treg на ОСК при раке молочной железы (РМЖ), колоректальном раке (КРР) и глиобластоме (ГБМ), результаты остаются фрагментарными и противоречивыми, что обусловило необходимость проведения данного аналитического обзора.*

***Цель исследования** – систематизация экспериментальных, обзорных и клинических данных о взаимодействии регуляторных Т-клеток и опухолевых стволовых клеток и формулировка гипотез, определяющих перспективные исследования и терапевтические подходы.*

***Методы:** Проведен комплексный поиск литературы в базах данных Medline (PubMed), NCBI, Google Scholar с 2015 по 2025 гг. При поиске использовались термины: «T-regulatory cells» и/или «cancer stem cells» и/или «breast cancer stem cells» и/или «colorectal cancer stem cells» и/или «glioma stem cells».*

***Результаты:** Обзор литературы показал, что Treg как непосредственно, так и опосредованно активируют ключевые сигнальные каскады (TGF-β/SMAD, NF-κB/CCL1, IL-10/STAT3), которые способствуют поддержанию стволового фенотипа опухолевых клеток и ассоциированы с неблагоприятным прогнозом при РМЖ, КРР и ГБМ.*

***Заключение:** Treg и опосредуемые ими молекулярные механизмы могут рассматриваться как потенциальные мишени для противоопухолевой терапии, однако их применение в клинической практике требует дальнейших экспериментальных и клинических исследований.*

***Ключевые слова:** Регуляторные Т-клетки (Treg), опухолевые стволовые клетки, стволовые клетки рака молочной железы, стволовые клетки колоректального рака, глиобластома, онкологические заболевания, онкоиммунология.*

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