UDC 616.345-006.6-04-076-092.6-085-089.86+612.017.1+576.385
DOI: 10.56871/RBR.2023.82.53.002

PATHOGENETIC SIGNIFICANCE OF *LAG-3* IN PATIENTS WITH COLORECTAL CANCER

© Andrey V. Chetveryakov, Victor L. Tsepelev

Chita State Medical Academy. Gorky str., 39a, Chita, Russian Federation, 672000

Contact information: Andrey V. Chetveryakov — Postgraduate Student, Department of Hospital Surgery. E-mail: yasnogorsk94@gmail.com
ORCID ID: 0000-0002-8472-107X

For citation: Chetveryakov AV, Tsepelev VL. Pathogenetic significance of *LAG-3* in patients with colorectal cancer // Russian biomedical research (St. Petersburg). 2023; 8(2): 12–17. DOI: https://doi.org/10.56871/RBR.2023.82.53.002

Received: 06.03.2023 **Revised: 05.04.2023** **Accepted: 10.05.2023**

Abstract. ***Background.*** The lymphocyte activation gene-3 (*LAG-3*) is involved in inhibiting the T-cell immune response. This mechanism is used by tumor cells to «escape» from immunity. The role of *LAG-3* in carcinogenesis at various localizations requires further research. ***Aim.*** We aimed to assess *LAG-3* level in blood serum and tumor tissue in patients with tumor of the colon. ***Materials and methods***. The study was carried out in the Regional Oncology Dispensary in Chita and included 44 patients with colorectal cancer and 25 patients with benign tumor of the colon who were treated between 2019 to 2020. The control group comprised 25 patients who had been operated due to colon injury at the Regional Clinical Hospital in Chita. We determined *LAG-3* concentration in blood serum, the supernatant of the homogenate of tumor tissue and lymph nodes using the flow cytofluometry method on the CytoFlex LX analyzer (Beckman Coulter, USA), using the LEGENDplex™ HU multiplex analysis kit (Immune Checkpoint, USA). The statistical significance of the differences was determined by the nonparametric Mann-Whitney U test. ***Results.*** The level of *LAG-3* in the blood serum of patients with colon cancer exceeded this indicator in the control group by 2.42 times ($p = 0.02$). The concentration of *LAG-3* in the blood serum of patients with colorectal cancer was 2.39 times higher ($p = 0.01$) compared to the group of patients with benign colon tumor. *LAG-3* level in tumor tissue in patients with colon cancer was 5.15 times higher ($p < 0.001$) than in the control group. The concentration of *LAG-3* in the lymph node tissue in patients with malignant neoplasm was 835.2 pg/ml. ***Conclusion.*** The data obtained demonstrated an increase in *LAG-3* level in blood serum in patients with colorectal cancer in comparison with the control group. There was also an increase in the concentration of LAG-3 in tumor tissue in patients with colorectal cancer. The obtained data can be used in the administration of targeted therapy for this group of patients.

Key words: colorectal cancer; *LAG-3*; immunity; immune control check points.

ПАТОГЕНЕТИЧЕСКОЕ ЗНАЧЕНИЕ *LAG-3* У ПАЦИЕНТОВ С КОЛОРЕКТАЛЬНЫМ РАКОМ

© Андрей Валерьевич Четверяков, Виктор Львович Цепелев

Читинская государственная медицинская академия. 672000, г. Чита, ул. Горького, 39а

Контактная информация: Андрей Валерьевич Четверяков — аспирант кафедры госпитальной хирургии. E-mail: yasnogorsk94@gmail.com
ORCID ID: 0000-0002-8472-107X

Для цитирования: Четверяков А.В., Цепелев В.Л. Патогенетическое значение *LAG-3* у пациентов с колоректальным раком // Российские биомедицинские исследования. 2023. Т. 8. № 2. С. 12–17. DOI: https://doi.org/10.56871/RBR.2023.82.53.002

Поступила: 06.03.2023 **Одобрена: 05.04.2023** **Принята к печати: 10.05.2023**

Резюме. ***Введение.*** Ген активации лимфоцитов-3 (Lymphocyte-activation gene 3, *LAG-3*) участвует в ингибировании Т-клеточного иммунного ответа. Данный механизм используют опухолевые клетки для «ускользания» от иммунного надзора. Роль *LAG-3* в канцерогенезе при различных локализациях требует дальнейшего изучения. ***Цель исследования.*** Оценка уровня *LAG-3* в сыворотке крови, ткани опухоли и лимфатических узлов

у пациентов с новообразованиями толстой кишки. ***Материалы и методы***. Под наблюдением находились 44 пациента с колоректальным раком, а также 25 больных с доброкачественными новообразованиями толстой кишки, проходивших лечение в ГУЗ «Краевой онкологический диспансер» г. Читы в период с 2019 по 2020 гг. Контрольная группа включала 25 пациентов, которым выполняли пластику колостомы, сформированной ранее по поводу травмы толстой кишки. Концентрацию *LAG-3* определяли в сыворотке крови, в супернатантегомогенате ткани опухоли и лимфатических узлов с помощью метода проточной цитофлуометрии. ***Результаты.*** Уровень *LAG-3* в сыворотке крови у пациентов с раком толстой кишки превышал данный показатель группы контроля в 2,42 раза ($p = 0,02$). Концентрация *LAG-3* в сыворотке крови у больных с колоректальным раком выше в 2,39 раза ($p = 0,01$) по отношению к группе пациентов с доброкачественной опухолью толстой кишки. Уровень *LAG-3* в ткани опухоли у пациентов с раком толстой кишки больше в 5,15 раза ($p < 0,001$), чем в группе контроля. Концентрация *LAG-3* в ткани лимфатических узлов у пациентов со злокачественным новообразованием составила 835,2 пг/мл. ***Заключение.*** Результаты исследований показывают увеличение уровня *LAG-3* в сыворотке крови у больных раком толстой кишки в сравнении с контрольной группой. Отмечено также увеличение концентрации *LAG-3* в ткани опухоли у пациентов с колоректальным раком. Полученные данные могут быть использованы при назначении таргетной терапии у данной категории больных.

Ключевые слова: колоректальный рак; *LAG-3*; иммунитет; иммунные контрольные точки.

INTRODUCTION

Nowadays, an active research on mechanisms of the inhibition of T-cell immune response in patient with malignant neoplasms of various localizations is providing. It has been established that this role is performed by immune checkpoints, which facilitate the “escape” of malignant cells from immune surveillance [1]. One of such molecules is Lymphocyte-activation gene 3 (*LAG-3*, CD223) [2, 3]. The expression of *LAG-3* is found on the surface of T-cells, natural killers (NK-cells) and dendritic cells (DCs). *LAG-3* connects with major histocompatibility complex-II (MHC-II) on the surface of antigen-presenting cells (APC). This eliminates the interaction of the T-cell receptor (TCR) with MHC-II and leads to suppression of T-cell activation [4]. It is noted, that *LAG-3* effectively prevents the development of autoimmune reactions. However, its unique and possibility to interact with MCH-II is used by tumour cells to “escape” the immune response [5]. Increased expression of *LAG-3* has been established in tumour tissue in patients with ovarian, gastric, breast, pancreatic cancer, and in patients with melanoma [6–8]. In the studies of R. Agocs (2021), data on increased expression of *LAG-3* in tumorous tissue in patients with colorectal cancer (CRC) was resaved. The author also noted that increased expression of this molecule may be used as prognostic marker. Further study of the role of *LAG-3* in carcinogenesis in CRC is relevant.

AIM

The aim of our research is to study the level of *LAG-3* in blood serum, tumorous tissue, lymph nodes in patient with neoplasms of the colon.

MATERIALS AND METHODS

The research was carried out in Regional Oncology Dispensary of Chita. 44 patients with colorectal cancer, and 25 patients with benign colon neoplasms took part in the study. All of them underwent treatment in 2019–2020. The control group included 25 patients who underwent treatment (plastic surgery of a colostomy formed earlier due to colon injuries) at the Regional Clinical Hospital in Chita. Patients were examined in accordance with clinical guidelines approved by the Ministry of Health of the Russian Federation [10]. The study was performed in accordance with the requirements of Ethics Committee of the Chita State Medical Academy of the Ministry of Health of the Russian Federation, as well as in accordance with the requirements of World Medical Association Declaration of Helsinki (2013). *The inclusion criterion* was the patient’s consent to participate in the study, and presence of a colon tumour. *The exclusion criteria* were patients with positive HIV status, autoimmune diseases, viral and bacterial infections, as well as patients who underwent chemotherapy or radiation therapy before surgery.

Histological examination revealed that in 39 cases (88.6 %) the tumour tissue was represented by moderately differentiated adenocarcinoma (G2), in three cases (6.8 %) it was a highly differentiated adenocarcinoma (G1), in two cases (4.6 %) it was a poorly differentiated adenocarcinoma (G3). Stage I of the process was diagnosed in 6 patients, stage II was in 24 cases, stage III was in 8 cases, and stage IV was in 6 patients.

Blood sampling was performed 2 hours before surgical treatment. Biopsy samples of tumour tissue and lymph nodes weighting up to 1g were homogenised using Ultra-Turrax T 10 basic (IKA, Germany) in phosphate buffered saline (pH 7.4).

Then this was centrifuged at 5000 rpm for 10 minutes and the supernatant was collected. The concentration of *LAG-3* in the blood serum and supernatant was determined by flow cytometry on a CytoFlex LX analyzer (Beckman Coulter, USA) using the LEGENDplex™ HU multiplex assay kit (Immune Checkpoint, USA) in accordance with the manufacturer's instructions.

When performing statistical processing, the International Committee of Medical Journal Editors (ICMJE) and Statistical Analyses and Methods in the Published Literature (SAMPL) were used [11, 12]. Nominal data was described with indication of absolute values and percentages. The results of the study were compared using the Pearson's chi-squared test. This allows one to assess the significance of differences between the actual number of outcomes or qualitative characteristics of the sample falling into each category and theoretical number that can be expected in the studied groups if the null hypothesis is true [13]. The normal distribution of quantitative characteristics in the groups of less than 50 people was assessed using Shapiro–Wilk test. Taking into account the distribution of characteristics that differed from normal in all groups, the obtained data were presented as a median, first and third quartiles: Me [Q1; Q3]. Kruskal–Wallis test (H-test) was performed to compare three independent groups for one quantitative trait. Then, in the presence of statistically significant differences, taking into account the Bonferroni correction, pairwise comparisons were performed using the Mann–Whitney U test [14]. To determine the actual degree of parallelism between the parameters under study, the Spearman rank correlation coefficient was used. The strength of the relationship between the studied parameters was determined using the Chaddock scale [15]. Statistical processing of the results was carried out using IBM SPSS Statistics Version 25.0 software package (International Business Machines Corporation, USA).

RESULTS

We have found that the level of *LAG-3* in blood serum of patient with colorectal cancer was 2.42 times higher than in controls [1.69; 3.44] (U = 273.5, p = 0.02). The level of *LAG-3* in blood serum of patients with CRC was 2.39 times higher [1.5; 3.29] than in patients with benign tumour of the colon (U = 266.0, p = 0.01). It should be noted, that the level of the molecule in controls and patients with benign tumour of the colon has no statistically significant differences (U = 189.0, p = 0,78) (Table 1).

Similar dynamics were observed when studying this molecule in neoplasm tissue. The level of *LAG-3* in tumorous tissue in patients with CRC was 5.15 times higher [4.09; 7.13] than in controls (U = 23.0, p < 0.001). The level of *LAG-3* in tumorous tissue in patient with CRC was 1.8 times higher [1.43; 2.58] than in patients with benign tumour of the colon (p = 0,008). In patients with CRC we determined the level of *LAG-3* in lymph nodes. The level was 835.2 [708.5; 1082.2] pg/ml.

DISCUSSION

Our studies showed that in patients with colon cancer, the concentration of the soluble form of *LAG-3* in the blood serum was higher than in controls and in group of patients with benign colon tumours. In the studies of Ying Peng (2022), increased level of this protein was noted in patients with non-small cell lung cancer [16], as well as in patients with gastric cancer [17]. We have noted similar dynamics of the *LAG-3* level in tumour tissue. Data on increased expression of *LAG-3* in tumorous tissue was registered in patients with B-cell lymphoma, lung and ovarian cancer [18].

Proteins MHC-II and fibrinogen-like protein 1 (FGL-1) are ligands for *LAG-3* [4]. At the early stages of ontogenesis, MHC-II recruits CD-4+ T-cells and enhances the antitumor immune response. At the same time, after connection of MHC-II and *LAG-3* immune suppression mechanisms are activated, and disruption in T-cells proliferation and cytokine secretions appears. It is known, that melanoma cells expressing MCH-II block CD4+ T-cell function, thereby evading recognition and destruction by the immune system

Table 1

***LAG-3* level in patients with colon tumor**

Таблица 1

Уровень *LAG-3* у больных с новообразованиями толстого кишечника

LAG-3 level (pg/ml)	Groups of patients			Test statistics, df = 2
	control group, n = 25	benign tumor, n = 25	colorectal cancer, n = 44	
Blood serum	15,0 [14,5; 20,8]	15,2 [15,1; 23,4]	36,3 [35,1; 49,7]	H = 9,3 p = 0,009
Tumor tissue	16,8 [16,5; 20,1]	46,4 [45,6; 57,5]	86,6 [82,3; 117,7]	H = 42,7 p < 0,001

Note: H — Kruskal-Wallis test; p — level of significance of differences.

[19, 20]. It is worth paying attention to the fact of high expression of *LAG-3* on tumour-infiltrating lymphocytes (TILs). In particular, high level of *LAG-3* expression was noted in patients with non-small cell lung cancer, sarcoma of soft tissue, ovarian cancer, melanoma [18, 21]. Increased expression of *LAG-3*, finding in T-cells, is a marker of aggressive course of malignant neoplasm. It affects survival and prognosis for patients [22]. Moreover, some authors noted the role of *LAG-3* in differentiation of T-reg cells, which contribute to the development of immunosuppression. At the same time, LAG-3 inhibits T-reg induction [23]. Of particular interest is the ability of the *LAG-3* molecule to interact with other immune checkpoints, particularly PD-1 (programmed cell death-1). This interaction results in a combined suppressive effect on the TCR and T-cell immune response as a whole [24].

So, our studies showed that *LAG-3* plays an important role in mechanisms of carcinogenesis and is a promising immunotherapeutic target for colorectal cancer.

CONCLUSION

The results demonstrate increased levels of *LAG-3* in blood serum and tumours tissue in patients with CRC compared to controls. The obtained data can be used when prescribing targeted therapy for this category of patients.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

REFERENCES

1. Klapholz M. Presence of Tim3 + and PD−1 + CD8 + T cells identifies microsatellite stable colorectal carcinomas with immune exhaustion and distinctclinicopathological features The Journal of Pathology. 2022. DOI: 10.1002/path.5877.
2. Liao X. A Review of emerging biomarkers for immune checkpoint inhibitors in tumors of the gastrointestinal tract. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2022; 28: e935348-1. DOI: 10.12659/MSM.935348.
3. Yadav D. Cancer immunotherapy by immune checkpoint blockade and its advanced application using bio-nanomaterials. Seminars in Cancer Biology. Academic Press. 2022.
4. Guy C., Mitrea D.M., Chou P.C. et al. LAG3 associates with TCR–CD3 complexes and suppresses signaling by driving co-receptor–Lck dissociation. Nature Immunology. 2022; 23(5): 757–67. DOI: 10.1038/s41590-022-01176-4.
5. Jonkman T.H., Dekkers K.F., Slieker R.C. et al. Functional genomics analysis identifies T and NK cell activation as a driver of epigenetic clock progression. Genome biology. 2022; 23(1): 1–21. DOI: 10.1186/s13059-021-02585-8.
6. Mehdizadeh S., Bayatipoor H., Pashangzadeh S. et al. Immune checkpoints and cancer development: Therapeutic implications and future directions. Pathol Res Pract. 2021; 223: 153485. DOI: 10.1016/j.prp.2021.153485.
7. Fucikova J. Immunological control of ovarian carcinoma by chemotherapy and targeted anticancer agents. Trends in Cancer. 2022; DOI: 10.1016/j.trecan.2022.01.010.
8. Zhou C. Monitoring pre-and post-operative immune alterations in patients with locoregional colorectal cancer who underwent laparoscopy by single-cell mass cytometry. Frontiers in immunology. 2022; 13: 807539–807539.
9. Rhyner Agocs G., Assarzadegan N., Kirsch R. et al. LAG-3 Expression Predicts Outcome in Stage II Colon Cancer. Journal of personalized medicine. 2021; 11(8): 749. DOI: 10.3390/jpm11080749.
10. Obshcherossiyskiy natsional'nyy soyuz. Assotsiatsiya onkologov Rossii. Zlokachestvennyye novoobrazovaniya obodochnoy kishki i rektosigmoidnogo otdela [Malignant neoplasms of the colon and rectosigmoid]. Klinicheskiye rekomendatsii. 2020. (in Russian).
11. Alshogran O.Y., Al-Delaimy W.K. Understanding of international committee of medical journal editor's authorship criteria among faculty members of pharmacy and other health sciences in Jordan. J Empir Res Hum Res Ethics. 2018; 13(3): 276-84. DOI: 10.1177/15562646187 64575.

12. Lang T.A., Altman D.G. Basic statistical reporting for articles published in biomedical journals: Statistical analyses and methods in the published literature or the SAMPL guidelines. IntJNursStud. 2015; 52(1): 5–9. DOI: 10.1016/j.ijnurstu.2014.09.006.
13. Mudrov V.A. Algoritmy statisticheskogo analiza kolichestvennykh priznakov v biomeditsinskikh issledovaniyakh s pomoshch'yu paketa programm SPSS [Algorithms for statistical analysis of quantitative traits in biomedical research using the SPSS software package]. Zabaykal'skiy meditsinskiy vestnik. 2020; 1: 140–50. (in Russian).
14. Mudrov V.A. Algoritmy statisticheskogo analiza kachestvennykh priznakov v biomeditsinskikh issledovaniyakh s pomoshch'yu paketa programm SPSS [Algorithms for statistical analysis of qualitative features in biomedical research using the SPSS software package]. Zabaykal'skiy meditsinskiy vestnik. 2020; 1: 151–63. (in Russian).
15. Mudrov V.A. Algoritmy korrelyatsionnogo analiza dannykh v biomeditsinskikh issledovaniyakh s pomoshch'yu paketa programm SPSS [Algorithms for correlation analysis of data in biomedical research using the SPSS software package]. Zabaykal'skiy meditsinskiy vestnik. 2020; 2: 169–76. (in Russian).
16. Peng Y., Zhang C., Rui Z. et al. A comprehensive profiling of soluble immune checkpoints from the sera of patients with non-small cell lung cancer. J Clin Lab Anal. 2022; 36(2): e24224. DOI: 10.1002/jcla.24224.
17. Li N. Soluble LAG-3 acts as a potential prognostic marker of gastric cancer and its positive correlation with CD8 + t cell frequency and secretion of IL-12 and INF-γ in peripheral blood. 2018; 341–51. DOI: 10.3233/CBM-181278.
18. Chen F. Immunohistochemistry analyses of LAG-3 expression across different tumor types and co-expression with PD-1. J Clin Oncol. 2020; 38(15): e15086–e15086. DOI: 10.1200/JCO.2020.38.15_suppl.e15086.
19. Baleeiro R.B., Bouwens C.J., Liu P. et al. MHC class II molecules on pancreatic cancer cells indicate a potential for neo-antigen-based immunotherapy. OncoImmunology. 2022; 11(1): 2080329. DOI: 10.1080/2162402x2022.2080329.
20. Pyke R.M. Evolutionary pressure against MHC class II binding cancer mutations. Cell. 018; 175(2): 416–28. DOI: 10.1016/j.cell.2018.08.048.
21. Karlsson J. Molecular profiling of driver events in metastatic uveal melanoma Nature communications. 2020; 11(1): 1–13.
22. Gertel S., Polachek A., Elkayam O. Lymphocyte activation gene-3 (LAG-3) regulatory T cells: An evolving biomarker for treatment response in autoimmune diseases. Autoimmunity Reviews. 2022; 21(6): 103085. DOI: 10.1016/j.autrev.2022.103085.
23. Tawbi H.A., Schadendorf D., Lipson E.J. et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. New England Journal of Medicine. 2021; 386(1): 24–34.
24. Edwards C.J., Sette A., Cox C. et al. The multi-specific VH-based Humabody CB213 co-targets PD1 and LAG3 on T cells to promote anti-tumour activity. British journal of cancer. 2022; 126(8): 1168–77. DOI: 10.1038/s41416-021-01684-4.

ЛИТЕРАТУРА

1. Klapholz M. Presence of Tim3 + and PD-1 + CD8 + T cells identifies microsatellite stable colorectal carcinomas with immune exhaustion and distinctclinicopathological features The Journal of Pathology. 2022. DOI: 10.1002/path.5877.
2. Liao X. A Review of emerging biomarkers for immune checkpoint inhibitors in tumors of the gastrointestinal tract. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2022; 28: e935348-1. DOI: 10.12659/MSM.935348.
3. Yadav D. Cancer immunotherapy by immune checkpoint blockade and its advanced application using bio-nanomaterials. Seminars in Cancer Biology. Academic Press. 2022.
4. Guy C., Mitrea D.M., Chou P.C. et al. LAG3 associates with TCR–CD3 complexes and suppresses signaling by driving co-receptor-Lck dissociation. Nature Immunology. 2022; 23(5): 757–67. DOI: 10.1038/s41590-022-01176-4.
5. Jonkman T.H., Dekkers K.F., Slieker R.C. et al. Functional genomics analysis identifies T and NK cell activation as a driver of epigenetic clock progression. Genome biology. 2022; 23(1): 1–21. DOI: 10.1186/s13059-021-02585-8.
6. Mehdizadeh S., Bayatipoor H., Pashangzadeh S. et al. Immune checkpoints and cancer development: Therapeutic implications and future directions. Pathol Res Pract. 2021; 223: 153485. DOI: 10.1016/j.prp.2021.153485.
7. Fucikova J. Immunological control of ovarian carcinoma by chemotherapy and targeted anticancer agents. Trends in Cancer. 2022; DOI: 10.1016/j.trecan.2022.01.010.
8. Zhou C. Monitoring pre-and post-operative immune alterations in patients with locoregional colorectal cancer who underwent laparoscopy by single-cell mass cytometry. Frontiers in immunology. 2022; 13: 807539–807539.
9. Rhyner Agocs G., Assarzadegan N., Kirsch R. et al. LAG-3 Expression Predicts Outcome in Stage II Colon Cancer. Journal of personalized medicine. 2021; 11(8): 749. DOI: 10.3390/jpm11080749.
10. Общероссийский национальный союз. Ассоциация онкологов России. Злокачественные новообразования ободочной кишки и ректосигмоидного отдела. Клинические рекомендации. 2020.
11. Alshogran O.Y., Al-Delaimy W.K. Understanding of international committee of medical journal editor's authorship criteria among faculty members of pharmacy and other health sciences in Jordan. J Empir Res Hum Res Ethics. 2018; 13(3): 276-84. DOI: 10.1177/15562646187 64575.
12. Lang T.A., Altman D.G. Basic statistical reporting for articles published in biomedical journals: Statistical analyses and methods in the published literature or the SAMPL guidelines. Int J Nurs Stud. 2015; 52(1): 5–9. DOI: 10.1016/j.ijnurstu.2014.09.006.

13. Мудров В.А. Алгоритмы статистического анализа количественных признаков в биомедицинских исследованиях с помощью пакета программ SPSS. Забайкальский медицинский вестник. 2020; 1: 140–50.
14. Мудров В.А. Алгоритмы статистического анализа качественных признаков в биомедицинских исследованиях с помощью пакета программ SPSS. Забайкальский медицинский вестник. 2020; 1: 151–63.
15. Мудров В.А. Алгоритмы корреляционного анализа данных в биомедицинских исследованиях с помощью пакета программ SPSS. Забайкальский медицинский вестник. 2020; 2: 169–76.
16. Peng Y., Zhang C., Rui Z. et al. A comprehensive profiling of soluble immune checkpoints from the sera of patients with non-small cell lung cancer. J Clin Lab Anal. 2022; 36(2): e24224. DOI: 10.1002/jcla.24224.
17. Li N. Soluble LAG-3 acts as a potential prognostic marker of gastric cancer and its positive correlation with CD8 + T cell frequency and secretion of IL-12 and INF-γ in peripheral blood. 2018; 341–51. DOI: 10.3233/CBM-181278.
18. Chen F. Immunohistochemistry analyses of LAG-3 expression across different tumor types and co-expression with PD-1. J Clin Oncol. 2020; 38(15): e15086–e15086. DOI: 10.1200/JCO.2020.38.15_suppl.e15086.
19. Baleeiro R.B., Bouwens C.J., Liu P. et al. MHC class II molecules on pancreatic cancer cells indicate a potential for neo-antigen-based immunotherapy. OncoImmunology. 2022; 11(1): 2080329. DOI: 10.1080/2162402x2022.2080329.
20. Pyke R.M. Evolutionary pressure against MHC class II binding cancer mutations. Cell. 018; 175(2): 416–28. DOI: 10.1016/j.cell.2018.08.048.
21. Karlsson J. Molecular profiling of driver events in metastatic uveal melanoma Nature communications. 2020; 11(1): 1–13.
22. Gertel S., Polachek A., Elkayam O. Lymphocyte activation gene-3 (LAG-3) regulatory T cells: An evolving biomarker for treatment response in autoimmune diseases. Autoimmunity Reviews. 2022; 21(6): 103085. DOI: 10.1016/j.autrev.2022.103085.
23. Tawbi H.A., Schadendorf D., Lipson E.J. et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. New England Journal of Medicine. 2021; 386(1): 24–34.
24. Edwards C.J., Sette A., Cox C. et al. The multi-specific VH-based Humabody CB213 co-targets PD1 and LAG3 on T cells to promote anti-tumour activity. British journal of cancer. 2022; 126(8): 1168–77. DOI: 10.1038/s41416-021-01684-4.