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The role of galectin-1 and galectin-3 in the mechanisms of T-cell immune response dysregulation in colon cancer

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ABSTRACT

The aim of the study was to characterize the features of the subpopulation composition and cytokine-secretory activity of T lymphocytes (Th1, Th17 and Treg) in relation to the concentration of galectin-1 and galectin-3 in the blood of patients with colon cancer.

Materials and methods. A total of 26 patients diagnosed with colon cancer were examined. The study material included whole peripheral blood, blood plasma, and supernatants of suspension cultures of mononuclear leukocytes. Lymphocytes isolated from blood were typed by flow cytometry using monoclonal antibodies. The content of galectin-1 and galectin-3 (in blood plasma) and IFNγ, IL-17A, and TGFβ (in supernatants of mononuclear leukocyte culture *in vitro*) were determined by enzyme-linked immunosorbent assay. The results obtained were analyzed by statistical methods.

Results. In patients with colon cancer, a significant increase in the concentration of galectin-1 and galectin-3 in the blood plasma was found, which was associated with a decrease in the content of CD4+T-bet+ Th1 lymphocytes, CD4+RORC2+ Th17 lymphocytes in the blood and *in vitro* hyposecretion of IL-17. At the same time, positive correlations were revealed between the concentration of galectin-1 and galectin-3, the content of CD4+FoxP3+ Treg cells in the blood, and the secretion of TGFβ by mononuclear leukocytes *in vitro*.

Conclusion. In colon cancer, increased levels of galectin-1 and galectin-3 in the blood are associated with quantitative deficiency and inhibited secretory activity of effector T-lymphocytes and activation of the immunosuppressive functions of regulatory T cells. These results suggest a negative role of galectin 1 and galectin 3 in the mechanisms of regulation of the T cell immune response in colon cancer.

Key words: galectins, T-lymphocytes, Th17, Treg, cytokines, immunosuppression, colon cancer.

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Conformity with the principles of ethics. All individuals included in the study signed an informed consent. The study was approved by the local Ethics Committee at Siberian State Medical University (Protocol No. 5309 of 22.05.2017).

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Роль галектина-1, -3 в механизмах дисрегуляции Т-клеточного звена иммунного ответа при раке толстого кишечника

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РЕЗЮМЕ

Цель исследования – охарактеризовать особенности субпопуляционного состава и цитокин-секреторной активности Т-лимфоцитов (Th1, Th17 и Treg) во взаимосвязи с концентрацией галектина-1 и галектина-3 в крови у больных раком толстого кишечника.

Материалы и методы. Обследованы 26 пациентов (14 мужчин и 12 женщин, средний возраст (62,9 ± 6,7) лет) с диагнозом рака толстого кишечника. В группу контроля вошли 17 здоровых доноров (11 мужчин и 6 женщин, средний возраст (58,2 ± 3,1) лет). Материалом исследования служила цельная периферическая кровь, плазма крови и супернатанты суспензионной культуры мононуклеарных лейкоцитов. Выделенные из крови лимфоциты типировали методом проточной лазерной цитофлуориметрии с использованием моноклональных антител. Методом иммуноферментного анализа определяли содержание галектина-1 и галектина-3 (в плазме крови) и IFNγ, IL-17A и TGFβ (в супернатантах культуры мононуклеарных лейкоцитов *in vitro*). Полученные результаты анализировали статистическими методами.

Результаты. У больных раком толстого кишечника установлено значимое увеличение концентрации галектина-1 и галектина-3 в плазме крови, ассоциированное со снижением содержания CD4+T-bet+ Th1-лимфоцитов, CD4+RORC2+ Th17-лимфоцитов в крови и гипосекрецией IL-17 лимфоцитами *in vitro.* Напротив, выявлена положительная корреляция между концентрацией галектинов 1 и 3, содержанием CD4+FoxP3+Treg клеток в крови и секрецией TGFβ мононуклеарными лейкоцитами *in vitro.*

Заключение. При раке толстого кишечника повышенный уровень галектинов 1 и 3 в крови сопряжен с количественным дефицитом и угнетением секреторной активности эффекторных Т-лимфоцитов, и, напротив, активацией иммуносупрессорных функций регуляторных Т-клеток. Полученные результаты указывают на негативную роль галектина-1 и галектина-3 в механизмах регуляции Т-клеточного звена иммунного ответа при раке толстого кишечника.

Ключевые слова: галектины, Т-лимфоциты, Th17, Treg, цитокины, иммуносупрессия, рак толстого кишечника.

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INTRODUCTION

Dysregulation of the antitumor immune response plays a pivotal role in the pathogenesis of malignancies and is typically represented by an imbalance of effector and regulatory T cells [1–3]. Throughout tumor progression, cancer cells obtain a variety of mechanisms that allow them to "program" their microenvironment and induce immunosuppression [4]. One of such mechanisms is tumor-associated production of galectins, galactoside-binding proteins with a wide spectrum of extra- and intracellular functions. [5, 6]. Among the galectin family, galectin-1 and galectin-3 were involved in the key stages of the tumor development, including malignant transformation, neoangiogenesis, invasion, metastasis, and modulation of the immune microenvironment [7, 8].

A number of *in vitro* studies have demonstrated that galectin-1 and galectin-3 are able to influence cell-mediated immune response by regulating differentiation and survival of type 1 and type 17 effector T-helper (Th) lymphocytes, as well as regulatory T-cells (Treg) with immunosuppressive phenotype [9–12]. Galectin-1 and galectin-3 expression by malignant cells and elements of the tumor microenvironment is considered to be one of the strategies to suppress antitumor immunity wielded by cancer cells [13, 14]. However, the features of the immunotropic effects of these galectins in tumor diseases remain understudied.

The aim of the study was to investigate the characteristics of subpopulation constitution and cytokine-secretory activity of blood T-lymphocytes (Th1, Th17, and Treg) in connection with the plasma concentration of galectin-1 and galectin-3 in patients with colon cancer.

MATERIALS AND METHODS

The study was carried out in the laboratory of clinical and experimental pathophysiology in the Pathophysiology Department, Siberian State Medical University (head – O.I. Urazova, Dr. Si. (Med.), Professor, Corresponding member of the RAS), and the Pathoanatomical Department of Tomsk Regional Oncological Dispensary (TROD) (head – I.L. Purlik, Dr. Si. (Med.)). The study included 26 patients diagnosed with colon cancer (14 men and 12 women, average age was 62.9 ± 6.7 years), who underwent treatment in the TROD (acting chief physician – M.Yu. Grishenko). The control group included 17 healthy donors consisting of 11 men and 6 women (average age was 58.2 ± 3.1 years). The criteria for exclusion of patients from the study were preoperative therapy, other malignancies, exacerbation of chronic diseases of an allergic, autoimmune, and infectious nature, and refusal to participate in the study. All patients were examined and operated on before the start of specific radiation and drug therapy.

The study material included whole peripheral blood collected from the median cubital vein on an empty stomach, blood plasma, as well as supernatants of the suspension cultures of mononuclear leukocytes. Isolation of mononuclear leukocytes from the whole blood was performed in the Ficoll-Paque density gradient centrifugation medium (p = 1,077 g/ml). The cultivation of mononuclear leukocytes was carried out in a complete nutrient medium RPMI-1640 in a CO2 incubator in a gas mixture containing 5% carbon dioxide at a temperature of 37 degrees Celsius for 48 hours. Measurement of the concentration of interferon (IFN) γ, transforming growth factor (TGF) β1, interleukin (IL) 17 in the supernatants of culture suspensions of mononuclear leukocytes, as well as levels of galectin-1 and galectin-3 in blood plasma was performed by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (BosterBio, USA; Vector-Best, Russia). Optical density was recorded on a Multiscan EX photometer-analyzer (Finland) at a wavelength of 450 nm.

To evaluate the content of CD4+T-bet+ (Th1), CD4+RORC2+ (Th17), and CD4+FoxP3+ (Treg) lymphocytes in the peripheral blood, expression of the surface receptor CD4 and intracellular transcription factors T-bet, RORC2, and FoxP3 in the whole blood was assessed by flow cytometry using monoclonal antibodies (PerCP-Cy5.5, Alexa Fluor 488, PE, APC; BD Biosciences, USA; RnD Systems, USA). Red blood cell lysis was performed using a BD Pharm Lyse lysing solution (BD Biosciences, USA). For fixation and permeabilization of cells for intranuclear staining, the Human FoxP3 Buffer Set (BD Biosciences, USA) was used. The stain Buffer (BD Biosciences, USA) was utilized to wash and resuspend cells.

Statistical processing of the results was carried out using Statistica 12.0 for Windows (StatSoft Inc., USA). Quantitative traits in the comparison groups were represented as the median (Me), upper (Q_1) and lower (Q_3) quartiles. The significance of differences in independent samples was evaluated with the nonparametric Mann–Whitney U-test. Correlation analysis was carried out us-

ing the Spearman rank correlation test. Differences were considered significant at $p < 0.05$.

RESULTS AND DICUSSION

The imbalance of the galectin expression in the tumor tissue and their concentration in the peripheral blood is characteristic of many malignant neoplasms and often correlates with the degree of tumor progression [15–17]. According to the literature, a high plasma level of galectin-1 in patients with colorectal cancer is associated with high aggressiveness of the tumor, advanced stages of the tumor process, and poor prognosis [18]. Some authors have noted a positive correlation of the level of galectin-3 expression by tumor cells with the stage of the disease and the presence of metastases [19, 20], while other authors, on the contrary, have reported a decrease in the expression of galectin-3 at the later stages of the tumor process [21, 22].

According to the results of ELISA, we found a significant increase in the concentration of galectin-1 and galectin-3 in blood plasma in patients with colon cancer compared with the corresponding values in healthy donors (Table 1).

Table 1

The content of galectin-1 and galectin-3 (ng/ml) in blood plasma in patients with colon cancer, *Me* (Q_1–Q_3)

Parameter	Patients with colon cancer	Healthy donors
Galectin-1	16.17 (15.31–17.10) $p = 0.0031$	13.74 (12.23–14.79)
Galectin-3	3.28 (2.30–5.71) $p = 0.0055$	1.56 (1.19-2.17)

Note. Level of significance of differences compared with corresponding indicators in healthy donors – p (here and Table 2,3).

High plasma levels of galectin-1 and glectin-3 are apparently the result of their over-expression by tumor cells and elements of the tumor microenvironment, which could in turn initiate an imbalance of individual subpopulations of T-lymphocytes in the development of antitumor immunity in colon cancer.

The key cells of antitumor resistance are CD4+ Th1 lymphocytes, which, via IFNγ secretion, activate cytotoxic CD8+ cells and stimulate the presentation of tumor-associated antigens by macrophages [23, 24]. CD4+ Th17 lymphocytes producing the IL-17A cytokine, on the one hand, increase the recruitment of cytotoxic lymphocytes and neutrophils in the tumor site and, on the other hand, induce tumor neoangiogenesis and formation of metastases [25, 26]. Regulatory T lymphocytes, characterized by secretion of the immunosuppressive cytokines IL-10 and TGFβ, are capable of inhibiting the antitumor immune response [27, 2].

An assessment of the subpopulation composition of peripheral blood T-lymphocytes in patients with colon cancer revealed a significant decrease in the relative content of CD4+T-bet+ Th1- and CD4+RORC2+ Th17 lymphocytes in comparison with corresponding parameters in healthy donors (Table 2). The percentage of CD4+FoxP+ Treg lymphocytes in blood, in contrast, exceeded the corresponding indicator in the control group (Table 2).

Table 2

Relative content of peripheral blood Th1, Th17, and Treg lymphocytes (% from the total lymphocytes population) in patients with colon cancer, *Me* (Q_1–Q_3)

Parameter	Patients with colon cancer	Healthy donors
Th1 (CD4+ T-bet+)	0.82 (0.24–0.94) $p = 0.0454$	1.24 (0.48–2.43)
Th17 (CD4+ RORC2+)	1.44 (0.19–2.13) $p = 0.0051$	3.51 (1.56–4.79)
Treg (CD4+ FoxP3+)	1.19 (0.8–1.48) $p = 0.0114$	0.55 (0.23–1.20)

The effect of galectin-1 and galectin-3 on individual subpopulations of helper T lymphocytes could be related to the heterogeneity of surface glycans, which are responsible for the binding of individual galectins, as well as the expression of cell surface glycoproteins that mediate lectin resistance [28, 29]. It is worth noting that galectin-1 and galectin-3 are able to exert a modulating effect not only on the proliferation and apoptosis of individual subpopulations of T-lymphocytes, but also on their cytokine-secretory activity.

According to our results, patients with colon cancer display a significant decrease in basal secretion of IL-17 by blood lymphocytes *in vitro* compared to healthy donors (Table 3). *In vitro* secretion of TGFβ1 by blood lymphocytes in the examined patients, in contrast, was 1.3 times higher than that in the control group. As for IFNγ, we did not find a significant difference in its basal secretion in patients with colon cancer relative to control values (Table 3).

Table 3

Secretion of cytokines in an in vitro culture of mononuclear leukocytes (pg/ml) in patients with colon cancer, *Me* (Q_1–Q_3)

Parameter	Patients with colon cancer	Healthy donors
IFNγ	1.286 (0.100–3.571)	1.429 (0.100–2.857)
IL-17	0.116 (0.100–0.425) $p = 0.0058$	0.657 (0.108–0.889)
TGFβ1	835.8 (534.3–1,949.0) $p = 0.0484$	628.6 (471.4–777.2)

To identify the relationship between the concentration of galectin-1 and galectin-3 in plasma and the identified structural and functional imbalance of CD4+ T lymphocytes, a correlation analysis was performed. In patients with colon cancer, negative correlations between the plasma concentration of galectin-1 and the relative content of CD4+T-bet+ Th1 lymphocytes (r =-0.56, p = 0.0353), CD4+RORC2+ Th17 lymphocytes (r = -0.59, p = 0.0334) and *in vitro* secretion of IL-17 (r = -0.63, p = 0.0013) were found. At the same time, a positive correlation was found between the plasma level of galectin-1 and the content of CD4+FoxP3+ Treg cells (r = 0.55, p = 0.0346) and basal secretion of TGFβ1 (r = 0.48, p = 0.0198). Similar results were obtained in an experimental *in vitro* study conducted by O.A.Vasilieva et al. (2015). Using the lymphocytes from healthy donors, the authors demonstrated the negative effect of recombinant galectin-1 on Th1- and Th17-mediated immune reactions with concomitant increase in Treg lymphocytes [28]. In turn, F. Cedeno-Laurent et al. (2012) demonstrated the ability of galectin-1, produced by malignant blood T-lymphocytes, to induce apoptosis of Th1 cells and, as a result, shift the Th1/Th2 balance towards Th2-dependent immune reactions and lower the effectiveness of antitumor resistance mechanisms in patients with skin T cell lymphoma [10].

According to *in vitro* studies, galectin-3 exerts dose-dependent stimulating effect on the differentiation and functional activity of Th17 lymphocytes, while inhibiting maturation and functions of Th1 and Treg cells [30]. This thesis is partially consistent with the results of our study, which established a negative correlation between the concentration of galectin-3 and the relative number of CD4+T-bet+ Th1 lymphocytes in the blood (r = –0.81, p = 0.0004). At the same time, we found a positive relationship between the plasma level of galectin-3 and basal secretion of TGFβ1 by peripheral blood lymphocytes (r = 0.70, p = 0.0001). The ability of galectin-3 to participate in the regulation of TGFβ1-associated signaling pathways was demonstrated by A.C. MacKinnon et al. (2012), who showed that specific inhibition of galectin-3 suppresses TGFβ1-dependent activation of β-catenin *in vitro* and *in vivo* [31].

Taken together, the results of the present study indicate the ability of galectin-1 and galectin-3 to modulate the functional activity of effector and regulatory blood T-lymphocytes in malignant neoplasms of the colon.

CONCLUSION

In patients with colon cancer, an increase in the concentration of galectin-1 and galectin-3 is associated with an imbalance of subpopulations of helper T-lymphocytes in the blood, inhibition of Th1- and Th17-dependent immune reactions, and activation of Treg lymphocytes with immunosuppressive properties. Tumor-associated production of galectin-1 and galectin-3 in colon cancer may represent one of the mechanisms by which tumor cells escape from immunological surveillance. The above said indicates the negative role of galectin-1 and galectin-3 in the mechanisms of regulation of the T cell immune response in colon cancer.

Further studies of the immunotropic effects of galectin-1 and galectin-3 on individual subpopulations of T lymphocytes will help to establish the relevance of these lectins as prognostic markers and advocate for the modulation of their activity in colon cancer.

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