

## **ФУНКЦИОНАЛЬНАЯ АКТИВНОСТЬ МОНОЦИТАРНОГО ЗВЕНА ИММУНИТЕТА ПРИ АДЕНОКАРЦИНОМЕ ЖЕЛУДКА**

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**Резюме.** Рак желудка входит в десятку по распространенности и занимает 4-е место по причинам смертности во всем мире. Наиболее распространенным и при этом самым агрессивным вариантом рака желудка является аденокарцинома (АКЖ). Моноцитарное звено иммунитета обеспечивают основную линию борьбы организма со злокачественными клетками, при этом у пациентов с АКЖ является недостаточно изученным.

Цель исследования — оценить показатели функциональной активности моноцитов у пациентов с аденокарциномой желудка на разных стадиях заболевания.

Обследовано 164 человека, среди которых 85 был поставлен диагноз аденокарцинома желудка I-IV стадии. Также в исследовании приняли участие 79 практически здоровых доноров. Функциональную активность и кислород-зависимый фагоцитоз моноцитов оценивали хемилюминесцентным методом. В качестве индуктора хемилюминесценции использовали люминол. Активация респираторного взрыва осуществлялась опсонизированным зимозаном.

У больных аденокарциномой желудка выявлено в состоянии покоя (спонтанная хемилюминесценция) увеличение показателей времени выхода кривой на максимум интенсивности хемилюминесценции ( $T_{max} = 7957$  с), площади под кривой хемилюминесценции ( $S_{cur} = 0,2 \times 10^6$ ), индекса активации (1,89 у. е.) и снижение максимального значения интенсивности хемилюминесценции ( $I_{max} = 424$  у. е.) относительно контрольной группой ( $T_{max} = 5533$  с,  $S_{cur} = 0,011 \times 10^6$ , индекс активации = 0,88 у. е.,  $I_{max} = 424$  у. е.,  $p < 0,05$ ). При индуцировании хемилюминесценции у больных АКЖ фиксируется статистически значимое преобладание  $S_{cur}$  ( $0,46 \times 10^6$ , в контрольной группе  $S_{cur} = 0,031 \times 10^6$ ). Также в группе пациентов с аденокарциномой желудка моноцитарный фагоцитоз снижен более чем в 2 раза (29% против 84% в контрольной группе,  $p < 0,05$ ). При анализе исследуемых параметров в зависимости от стадии заболевания было установлено, что нарушение хемилюминесцентной реакции у больных аденокарциномой желудка фиксируется уже на ранней стадии. При этом у больных с IV стадией аденокарциномы желудка показатели спонтанной и индуцированной хемилюминесценции более чем в 2 раза отличаются от показателей контрольной группы и пациентов на I стадии заболевания. Выявленные особенности свидетельствует о снижении эффективности иммунных реакций моноцитар-

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ного звена при аденокарциноме желудка уже на ранних стадиях заболевания и могут использоваться для выявления ранних признаков иммунных нарушений и оптимизации терапевтических подходов при данном заболевании.

*Ключевые слова:* аденокарцинома желудка, моноциты, хемилюминесцентная активность, иммунитет, иммунодефицит, макрофаги

## FUNCTIONAL ACTIVITY OF THE MONOCYTE IMMUNE LINK IN GASTRIC ADENOCARCINOMA

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**Abstract.** Stomach cancer is in the top ten in terms of prevalence and ranks 4<sup>th</sup> in terms of causes of death worldwide. The most common and most aggressive variant of gastric cancer is adenocarcinoma. The monocytic link of immunity provides the main line of the body's fight against malignant cells, while in patients with adenocarcinoma it is insufficiently studied. The purpose of the study was to evaluate the functional activity of monocytes in patients with gastric adenocarcinoma at different stages of the disease.

Individuals (n = 164) were examined, among whom 85 were diagnosed with stage I-IV stomach adenocarcinoma. The study also involved 79 apparently healthy donors. The functional activity and oxygen-dependent phagocytosis of monocytes were assessed by the chemiluminescent method. Luminol was used as a chemiluminescence inducer. The respiratory burst was activated with opsonized zymosan.

In patients with stomach adenocarcinoma, at rest (spontaneous chemiluminescence), an increase in the time the curve reached the maximum intensity of chemiluminescence ( $T_{max} = 7957$  s), the area under the chemiluminescence curve ( $S_{cur} = 0.2 \times 10^6$ ), the activation index (1.89 c. u.) and a decrease in the maximum value of chemiluminescence intensity ( $I_{max} = 424$  c. u.) relative to the control group ( $T_{max} = 5533$  s,  $S_{cur} = 0.011 \times 10^6$ , activation index = 0.88 c. u.,  $I_{max} = 424$  c. u.,  $p < 0.05$ ) were seen. When chemiluminescence is induced in patients with stomach adenocarcinoma, a statistically significant predominance of  $S_{cur}$  is fixed ( $0.46 \times 10^6$ , in the control group  $S_{cur} = 0.031 \times 10^6$ ). Also, in the group of patients with stomach adenocarcinoma, monocytic phagocytosis was reduced by more than 2 times (29% vs 84% in the control group,  $p < 0.05$ ). When analyzing the studied parameters, depending on the stage of the disease, it was found that the violation of the chemiluminescent reaction in patients with stomach adenocarcinoma is fixed already at an early stage. At the same time, in patients with stage IV stomach adenocarcinoma, the indicators of spontaneous and induced chemiluminescence are more than 2 times different from those in the control group and patients at stage I of the disease. The identified features indicate a decrease in the effectiveness of immune reactions of the monocytic link in stomach adenocarcinoma already in the early stages of the disease and can be used to detect early signs of immune disorders and optimize therapeutic approaches in this disease.

*Keywords:* gastric adenocarcinoma, monocytes, chemiluminescent activity, immunity, immunodeficiency, macrophages

### Introduction

Oncological diseases remain one of the most pressing socioeconomic problems worldwide [11]. According to the WHO for 2020, stomach cancer is among the ten most common and ranks 4<sup>th</sup> in terms of causes of death worldwide [12]. And although in the developed countries of the world there has been a trend towards a decrease in the incidence of this pathology, in developing countries, stomach cancer continues to occupy a leading position in terms of

mortality among oncological diseases. Stomach cancer has a low survival rate due to late diagnosis, with survival rates directly correlated with the stage of the disease. Russia is among the top three countries in terms of morbidity and mortality for this disease. Also, for stomach cancer, pronounced regional variability is characteristic. According to MSROI named after P.A. Herzen for 2020, the highest percentage of the prevalence of this disease is recorded in the Central, Volga and Siberian federal districts, while this disease is least common in the North Caucasian and Far

Eastern regions. The Krasnoyarsk Territory among the territories of the Siberian federal district is the leader in terms of incidence of stomach cancer [7]. Currently, the mechanisms of the pathogenesis of gastric cancer remain poorly understood. The etiology of this disease is characterized by multifactoriality, with special attention being paid to the infection of the body with *Helicobacter pylori*, recognized by WHO as a carcinogen [6]. Adenocarcinoma is the most common and aggressive type of stomach cancer [1, 4].

The immune system, and primarily phagocytic leukocytes, provide the body's main line of defense against malignant cells. The monocyte is the most active phagocyte in peripheral blood, with a phagocytic index approximately 3 times higher than that of neutrophils. A distinctive feature of monocytes is their high activity in an acidic environment, as well as the preservation of viability after the phagocytization process. Monocytes perform various functions – cytokine production, pathogen clearance, antigen presentation, are involved in wound healing and providing pro- and antitumor response [2] chemiluminescent activity. Chemiluminescent analysis is based on the registration of the emission of light quanta caused by the production of free radicals and reactive oxygen species by phagocytic cells at rest (spontaneous chemiluminescence), as well as in response to a stimulus or stimulus (induced chemiluminescence). There are works in the literature devoted to the chemiluminescent activity of neutrophils in various malignant diseases, however, such studies on monocytes in stomach adenocarcinoma are rare. Given the asymptomatic nature of the course of stomach cancer in the early stages, the identification of markers of impaired immune response, including the phagocytic activity of monocytes, can expand laboratory capabilities for detecting this malignant disease during population screening.

**The aim of the study** was to evaluate the features of the functional activity of monocytes in stomach cancer, depending on the stage of the disease.

## Materials and methods

As part of the goal, 164 people were examined, of which 85 were patients with stomach adenocarcinoma (SAC) aged 22-69 years. The control group consisted of 79 practically healthy donors without gastroenterological complaints (aged 20-68 years). Diagnosis of stomach adenocarcinoma was carried out by oncologists in the Krasnoyarsk regional oncological dispensary on the basis of a comprehensive instrumental and morphological examination. The study included patients with SAC stages I, II, III, IV.

The study was conducted with the permission of the Ethics Committee of the FRC KSC SB RAS (protocol no. 4 dated 02.08.2019). In working with

the examined patients, the ethical principles required by article 24 of the Constitution of the Russian Federation and the Declaration of Helsinki by the World Medical Association. Each participant signed an informed consent form for the study confirming their voluntary participation in the study.

Venous blood for research was taken in the morning from 8 to 9 o'clock, on an empty stomach, from the cubital vein, into vacutainer tubes with sodium heparin solution (5 U/mL). Peripheral blood monocytes were obtained by the standard method of adhesion to flat surfaces from mononuclear cells isolated from heparinized venous blood by ficollurografin density gradient centrifugation ( $\rho = 1.077$ ).

The assessment of spontaneous and induced chemiluminescence of monocytes was carried out for 90 minutes on a 36-channel CL 3606 chemiluminescent analyzer (Russia). The study of oxygen-dependent phagocytosis of blood monocytes was also carried out by the chemiluminescent method. The following characteristics were determined: the time of appearance of the chemiluminescence intensity maximum (Tmax), the maximum value of the chemiluminescence intensity (Imax), and the area of the chemiluminescence curve (S). Luminol was used as a chemiluminescence enhancer. Opsonized zymosan served as the respiratory burst inducer. The enhancement of chemiluminescence induced by opsonized zymosan was estimated by the ratio of the area of induced (S induced) to the area of spontaneous (S spont.) chemiluminescence and was designated by the activation index. Statistical data processing was carried out using the Statistica for Windows 8.0 (StatSoft Inc., USA, 2008) and Microsoft Excel 2007 (Microsoft, USA) application packages. Processing of the received data included calculation of non-parametric data: median (Me) and quartiles (Q<sub>0.25</sub>-Q<sub>0.75</sub>). Statistical differences between the data were assessed using the nonparametric Mann–Whitney U test. The critical level of significance when testing statistical hypotheses was taken equal to  $p < 0.05$ .

## Results and discussion

The study of the chemiluminescent activity (CA) of monocytes will allow us to evaluate the characteristics of a respiratory burst in a spontaneous and induced state in stomach adenocarcinoma. It is believed that the functional activity of phagocytes depends on CA, the higher the chemiluminescent activity, the greater the functional ability of the cells.

At the first stage, the chemiluminescent activity of monocytes was studied in patients with gastric adenocarcinoma relative to the control group (Table 1). It was found that the index of maximum intensity (Imax) during spontaneous chemiluminescence is lower compared to the control

TABLE 1. PARAMETERS OF THE CHEMILUMINESCENT REACTION OF MONOCYTES IN PATIENTS WITH STOMACH ADENOCARCINOMA (SAC) COMPARED WITH THE CONTROL GROUP, Me (Q<sub>0.25</sub>-Q<sub>0.75</sub>)

Indicator	Patients with SAC (n = 85)	Control group (n = 79)
Imax spontaneous, c. u.	424* (295.6-614.7)	486 (77.7-690.4)
Tmax spontaneous, s	7957* (7313-10465)	5533 (3505-9992)
Squr spontaneous (× 10 <sup>6</sup> )	0.2* (0.140-0.305)	0.011 (0.006-0.022)
Imax induced, c. u.	1183 (657-1284)	1395.6 (412.9-1637.3)
Tmax induced, s	5496 (5085-5869)	5485 (3104-6185)
Squr induced (× 10 <sup>6</sup> )	0.46* (0.39-0.96)	0.031 (0.01-0.07)
Activation index	1.89* (0.91-2.07)	0.88 (0.6-1.3)
Monocytic phagocytosis	29%±5% *	84%±7%

Note. \*, statistically significant differences between the indices of patients with stomach cancer and the control group (p < 0.001).

TABLE 2. INDICATORS OF SPONTANEOUS AND INDUCED CHEMILUMINESCENT RESPONSE OF MONOCYTES IN PATIENTS WITH STOMACH ADENOCARCINOMA (SAC) COMPARED WITH THE CONTROL GROUP, Me (Q<sub>0.25</sub>-Q<sub>0.75</sub>)

Indicator	Control group (n = 79)	SAC I stage (n = 19)	SAC II stage (n = 22)	SAC III stage (n = 24)	SAC IV stage (n = 20)
	1	2	3	4	5
Imax spontan., c. u.	486.8 (77.7-690.4)	454 (342-597)	425 (296-615)	390 (305-506)	362 (280-477)
					p <sub>1-5</sub> < 0.05
Tmax spontan., s	5523 (3505-9992)	6401 (6355-10060)	7951 (7313-10465)	9057 (7678-11263)	9285 (7569-11406)
		p <sub>1-2</sub> < 0.001	p <sub>1-3</sub> < 0.001	p <sub>1-4</sub> < 0.001	p <sub>1-5</sub> < 0.001 p <sub>2-5</sub> < 0.05
Squr spontan. (× 10 <sup>6</sup> )	0.01 (0.006-0.022)	0.12 (0.099-0.240)	0.20 (0.14-0.30)	0.29 (0.20-0.34)	0.33 (0.21-0.37)
		p <sub>1-2</sub> < 0.001	p <sub>1-3</sub> < 0.001	p <sub>1-4</sub> < 0.001	p <sub>1-5</sub> < 0.05 p <sub>2-5</sub> < 0.001
Imax induced, c. u.	1375.6 (412.0-1637.3)	1077 (819-1202)	1173 (657-1284)	1186 (1101-1324)	1181 (956-1425)
Tmax induced, s	5385 (3104-6185)	5584 (5499-6977)	5436 (5085-5869)	5768 (5288-6497)	5850 (5070-6719)
Squr induced (× 10 <sup>6</sup> )	0.03 (0.01-0.07)	0.34 (0.29-0.38)	0.44 (0.39-0.95)	0.69 (0.6-0.7)	0.72 (0.66-0.77)
		p <sub>1-2</sub> < 0.001	p <sub>1-3</sub> < 0.001	p <sub>1-4</sub> < 0.001	p <sub>1-5</sub> < 0.001 p <sub>2-5</sub> < 0.05
Activation index, c. u.	0.86 (0.6-1.3)	1.7 (1.4-2.2)	1.79 (0.90-2.06)	2.0 (1.90-2.27)	2.4 (2.0-2.6)
		p <sub>1-2</sub> < 0.001	p <sub>1-3</sub> < 0.001	p <sub>1-4</sub> < 0.001	p <sub>1-5</sub> < 0.001

group, which characterizes the low functionality of monofilaments in SAC. The time for the appearance of the spontaneous chemiluminescence maximum (Tmax) in patients with stomach adenocarcinoma is higher than in the control group, which indicates a prolongation of the time required for monocyte activation. The area under the curve of spontaneous and induced chemiluminescence (CL), as well as the activation index, were also increased in patients with SAC relative to the control. When studying the phagocytic activity of monocytes in patients with stomach adenocarcinoma, a decrease in the number of functionally mature phagocytic cells relative to the control group was recorded (Table 1).

In the second stage, the indicators of the chemiluminescent activity of monocytes in patients with stomach adenocarcinoma depending on the stage of the disease were studied (Table 2). The index of maximum intensity (Imax) in spontaneous CL of monocytes decreased in proportion to the stage of the disease, reaching statistical significance in stage IV of SAC relative to the control group. The Tmax of spontaneous CL, Sqr of spontaneous and induced CL, as well as the monocyte activation index, on the contrary, progressively increased from stage I to stage IV of stomach adenocarcinoma, exceeding the control group by more than two times at the last stage ( $p < 0.05$ ). Statistical differences between the studied parameters between I and IV stages of SAC were also revealed ( $p < 0.05$ ) (Table 2).

The development of stomach adenocarcinoma is promoted by many etiological factors, accompanied by the development of inflammatory and atrophic changes in the gastric mucosa [3, 6, 8]. The literature presents studies of the state of the immune system in

patients with atrophic gastritis, during which activation of cellular and humoral immunity was revealed [5, 10]. According to the authors, the activation of immunity in gastritis is aimed at eliminating concomitant infectious agents and destructive changes in mucosal cells. If we assume that atrophic gastritis can transform into a malignant state, then the decrease in immunological reactions in stomach adenocarcinoma may, on the one hand, be a consequence of the depletion of the internal reserves of the immune system, on the other hand, be an additional factor in the transformation of healthy cells of the gastric mucosa into malignant ones with prolonged exposure to risk factors. Changes in the immune system can also contribute to oxidative stress in the blood plasma, which is detected in both atrophic and malignant pathological conditions of the stomach [3, 9].

## Conclusion

The study made it possible to identify pronounced dysfunctions of the monocytic link of the immune systems in stomach adenocarcinoma already in the early stages of the disease. The syndrome of immune deficiency in tumor diseases is a nonspecific and universal link in the pathological process, which is once again confirmed by our results. Therefore, signs of immune deficiency in the presence of symptoms of gastric pathology increase the likelihood of detecting stomach cancer at an early stage. Given the high prevalence and significance of this disease, a study to identify the pathogenetic mechanisms of the formation and progression of stomach adenocarcinoma can contribute to the expansion of diagnostic approaches and optimization of therapeutic treatment.

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