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ИЗМЕНЕНИЕ ПЕЧЕНОЧНОЙ ЭКСПРЕССИИ ГЕНА *SOD1* В ПАТОГЕНЕЗЕ НАЖБП ПРИ ОЖИРЕНИИ

Комар А.А., Шункина (Скуратовская) Д.А., Вульф М.А., Ву Х.К., Тодосенко Н.М., Затолокин П.А., Кириенкова Е.В., Газатова Н.Д., Литвинова Л.С.

ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия

Резюме. Стеатоз в печени при ожирении увеличивает работу митохондрий по утилизации избыточных липидов. Перегрузка β-окисления жирных кислот, цикла трикарбоновых кислот и окислительного фосфорилирования приводит к снижению уровня АТФ и повышению образования активных форм кислорода. В норме, митохондрии способны эффективно удалять повышенный уровень активных форм кислорода с помощью антиоксидантной системы и метаболической адаптации клетки к измененным условиям. Целью данного исследования явилось изучение роли печеночной экспрессии *SOD* в патогенезе НАЖБП при ожирении. Было выявлено, что уровень экспрессии *SOD1* в печени у больных ожирением с и без СД 2 типа с ИМТ > 40 кг/м^2 был ниже, чем у здоровых доноров. Число копий митохондриальной ДНК (мтДНК) в печени у всех больных ожирением было ниже более чем в два раза относительно значений контрольной группы. В печени у больных ожирением без СД 2 типа уровень белка SOD1 и число копий мтДНК были взаимосвязаны между собой и отрицательно коррелировали с площадью жировых включений. Таким образом, у больных ожирением снижение антиоксидантной защиты в печени приводит к уязвимости митохондрий, что, в свою очередь, способствует прогрессированию стеатоза и инсулинорезистентности.

Ключевые слова: ожирение, СД 2 типа, супероксиддисмутаза, мтДНК, печень, стеатоз

HEPATIC *SOD1* GENE EXPRESSION CHANGES IN THE NAFLD PATHOGENESIS IN OBESITY

Komar A.A., Shunkina (Skuratovsvkaia) D.A., Vulf M.A., Vu H.Q., Todosenko N.M., Zatolokin P.A., Kirienkova E.V., Gazatova N.D., Litvinova L.S.

Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation

Abstract. Steatosis in the liver in obesity increases the work of mitochondria to utilize excess lipids. An overload of β-oxidation of fatty acids, the tricarboxylic acid cycle, and oxidative phosphorylation leads to a decrease in ATP and an increase in the formation of reactive oxygen species. Normally, mitochondria can efficiently remove elevated levels of reactive oxygen species using the cell's antioxidant system and metabolic

Адрес для переписки:

Комар Александра Андреевна
ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия
236001, Россия, г. Калининград, ул. Гайдара, 6, НТП «Фабрика».
Тел.: 8 (963) 295-77-74
E-mail: alexandkomar@gmail.com

Address for correspondence:

Komar Aleksandra A.
Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation
236001, Russian Federation, Kaliningrad, Gaidar str., 6, STP "Fabrika".
Phone: 7 (963) 295-77-74
E-mail: alexandkomar@gmail.com

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adaptation to altered conditions. This study aimed to investigate the role of hepatic *SOD* expression in the pathogenesis of NAFLD in obesity. It was found that the level of *SOD1* expression in the liver in obese patients with and without type 2 diabetes with a BMI > 40 kg/m^2 was lower than in healthy donors. The copy number of mitochondrial DNA (mtDNA) in the liver in all obese patients was more than two times lower than in the control group. In the liver of obese patients without type 2 diabetes, the SOD1 protein level and the mtDNA copy number were interrelated and negatively correlated with the area of fatty inclusions. Thus, in obese patients, a decrease in antioxidant defense in the liver leads to the vulnerability of mitochondria, which, in turn, contributes to the progression of steatosis and insulin resistance.

Keywords: obesity, T2DM, superoxide dismutase, mtDNA, liver, steatosis

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Introduction

Insulin resistance, oxidative stress, and inflammation play a central role in the non-alcoholic fatty liver disease (NAFLD) pathogenesis [3] liver cancer, and indications for orthotopic liver transplantation. Given its high prevalence, the absence of FDA-approved drugs for NAFLD is noticeable. In the pathogenesis of NAFLD, it is well known that mitochondrial dysfunction arises as a result of changes in ETC complexes and the membrane potential (Δψm. Although the pathogenesis of lipid accumulation in the liver has been described, the molecular mechanisms behind transition of steatosis to inflammation and fibrosis are still poorly understood. Decreased ability to oxidize fatty acids, increased delivery and transport of free fatty acids (FFA), as well as increased fatty acid production in the liver are considered important factors of hepatocyte damage in obesity [3] liver cancer, and indications for orthotopic liver transplantation. Given its high prevalence, the absence of FDA-approved drugs for NAFLD is noticeable. In the pathogenesis of NAFLD, it is well known that mitochondrial dysfunction arises as a result of changes in ETC complexes and the membrane potential (Δψm. Mitochondrial dysfunction in NAFLD is accompanied by incomplete/suboptimal fat oxidation, which leads to the accumulation of toxic lipid intermediates such as ceramides and diacylglycerol, which can cause inflammation and disrupt insulin signaling [6]. Also, hepatocyte mitochondrial respiratory chain overload in obesity promotes formation of reactive oxygen species (ROS) [6].

In normal physiological conditions, cellular ROS are found at minimal concentration as byproducts of aerobic metabolism and secondary messengers in many signaling pathways. Moreover, there is a stable balance between prooxidants and antioxidants in normal physiological conditions [4]. However, while rate of free radical formation exceeds the capacity of antioxidant protection, oxidative stress develops, followed by serious damage to the cellular apparatus [4]. The cell has several defense and repair mechanisms counterbalancing oxidative stress. However, it has been shown that antioxidant enzymes superoxide dismutase (SOD), catalase, glutathione (GSH), glutathione peroxidase (GSHPx), and glutathione reductase (GSHR) exhibit decreased activity in the affected brain areas during neurodegenerative diseases [5]. It is likely that in NAFLD, the defense system is also affected and cannot cope with a large number of errors in lipid metabolism, which aggravates the disease course and progression. Thus, the was study aimed to study a role of hepatic *SOD1* expression in the NAFLD pathogenesis in obesity.

Materials and methods

166 obese patients were included in the study group. Of these, 28 patients (9 men, 19 women) with obesity without type 2 diabetes (T2DM) and body mass index (BMI) < 40 kg/m^2 (group 2) (age 42±10 years; BMI 35.2±2.9 kg/m^2), 47 patients (14 men, 33 women) with obesity without T2DM and BMI > 40 kg/m^2 – group 3 (age 45±9 years; BMI 48.6±8.0 kg/m^2). Groups 4 and 5 included obese patients with T2DM – 21 patients (8 males, 13 females) with BMI < 40 kg/m^2 (age 46±10 years; BMI 36.5±3.0 kg/m^2) and 45 patients (12 males, 33 females) with a BMI > 40 kg/m^2 (age 48±8 years; BMI 50.2±8.2 kg/m^2). 25 (15 males; 10 females) apparently healthy donors with normal anthropometric and biochemical parameters (age 38±9 years; BMI 22.7±3.7 kg/m^2) were included in the control group (group 1). These groups were age- and sex-comparable. The diagnosis of T2DM was established based on examination at specialized hospital, guided by the diagnostic criteria for diabetes mellitus and other types of hyperglycemia of the World Health Organization (1999-2013) (IDF, 2013). Venous blood (Vacuette with a clot activator or EDTA) samples were used for biochemical and serological assays. Liver biopsies were collected during elective bariatric surgery and used to study gene expression, protein production, mitochondrial DNA (mtDNA), and histological analysis. Voluntary informed consent for the study was signed and provided by all patients. Permission to conduct the study was obtained from the local ethics committee (Protocol No. 2 of IKBFU, March 6, 2017).

The serum glucose level was determined on an automatic biochemical analyzer CA-180 (FURUNO ELECTRIC CO., LTD, Japan), using commercial kits (Dia-m, Russia). Plasma insulin levels were determined by flow fluorimetry using commercial test systems (Bio-Plex, Pro Human Diabetes 10-Plex Assay, Bio-Rad, USA) on an automated analyzer (Bio-Plex® 200 Systems, Bio-Rad, USA) and Bio-Plex Manager software (Bio-Rad, USA). Insulin values were converted from pg/ml to miU/ml by using an online calculator (http://www.endmemo.com/medical/unitconvert/Estradiol.php). The insulin resistance index was calculated by using an online software (https://www.omnicalculator.com/health/homa-ir).

Total RNA from liver biopsies was isolated by using the ExtractRNA reagent (Evrogen, Russia). Reverse transcription of RNA samples was performed using the MMLV RT kit (Evrogen, Russia). Complementary DNA (cDNA) synthesis was performed according to the manufacturer's protocol. SOD1 gene expression was determined by quantitative PCR using qPCRmix-HS reagents (Evrogen, Russia) on a CFX96 amplifier (Bio-Rad, USA). Protein fraction from liver biopsies was isolated by using RIPA buffer (RIPA Buffer, Termo Scientific, USA), and concentration measurement was performed by the Bradford method (BCA Protein Assay Kit, ThermoFisher, USA). Semi-quantitative analysis of protein production in liver biopsies was performed by running immunoblotting assay to confirm results of gene expression. Semi-quantitative protein measurement was carried out by using specific monoclonal antibodies to SOD1 (Invitrogen, USA) and GAPDH (Thermo Fisher, USA); and blotting systems (Mini-PROTEAN Tetra Systems, Trans-Blot Turbo, Bio-Rad, USA). The target proteins were detected on a ChemiDoc MP Imaging System (BioRad, USA). Membrane images were analyzed using the software ImageLab, Bio-Rad. The liver mtDNA copy number was estimated by Droplet Digital PCR (ddPCR) using the QX200 Droplet Digital PCR System (BioRad, USA). A detailed protocol is available in study published earlier (https://pubmed.ncbi.nlm.nih.gov/29429383/).

The data were analyzed for normal distribution using the Kolmogorov-Smirnov test. Differences were assessed using Student's t-test for normal distribution (two groups, parametric test) and Mann-Whitney test for abnormal distribution (two groups, nonparametric test). Data are presented as mean and standard deviation as well as median and 25%-75% quartiles. The analysis of relationship between two variable was carried out using the Spearman correlation method. Statistical significance was set at $p < 0.05$ level.

Results and discussion

NAFLD is a liver disease that begins with steatosis and progresses to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma [6]. The liver is central to the intermediate metabolism of glucose, lipids, and ketones, which are needed to meet the energy requirements in peripheral tissues, heart, and brain. Triglycerides and free fatty acids accumulate in excess in the liver during obesity and insulin resistance, which leads to the formation of lipid droplets in hepatocytes. In turn, steatosis increases β-oxidation of fatty acids, induces the tricarboxylic acid cycle, and stimulates oxidative phosphorylation [6]. Overloading these processes leads to decreased ATP level, increased formation of reactive oxygen species (ROS), and excessive fat deposition [6]. Oxidative stress is one of the key mediators of liver damage and is the main contributor to the progression from steatosis to steatohepatitis [1]. In normal physiological conditions, mitochondria can efficiently remove elevated ROS levels via the antioxidant system and cell metabolic adaptation to altered conditions [1]. However, ROS production is too high so that compensatory mechanisms cannot cope with such a load during NAFLD. Superoxide dismutase-1 (SOD1) is a well-known intracellular antioxidant enzyme. Intracellular SOD1 (cytosolic Cu/ZnSOD) is a homodimer (32 kDa) mainly localized in the cytosol, as well as in the intermembrane space of mitochondria [2] especially superoxide anion ($O2 \bullet -$. Presumably, SOD1 may play a role in NAFLD. Thus, monitoring changes in hepatic *SOD1* expression in NAFLD will help to understand the antioxidant system state.

Plasma glucose levels in obese patients without T2DM with BMI < 40 kg/m^2 exceeded those in control group ($p = 0.006$) (Table 1). Plasma glucose levels in obese patients with T2DM (with BMI < 40 kg/m^2 and BMI > 40 kg/m^2) were significantly higher than in the control group ($p < 0.001$), obese patients without T2DM ($p = 0.007$ and $p < 0.001$, respectively) with BMI < 40 kg/m^2 and BMI > 40 kg/m^2 ($p < 0.001$) (Table 1). As expected, glucose levels went outside the reference range (3.9-6.4 mmol/l) only in obese patients with T2DM (Table 1). Plasma insulin levels in obese patients without T2DM with BMI > 40 kg/m^2 exceeded those in control group ($p = 0.003$) (Table 1). Plasma insulin levels in obese patients with T2DM (with BMI < 40 kg/m^2 and BMI > 40 kg/m^2) were significantly higher than in the control group ($p < 0.001$), obese patients without T2DM ($p = 0.01$ and $p = 0.03$, respectively) with BMI < 40 kg/m^2 and BMI > 40 kg/m^2 ($p = 0.004$ and $p = 0.02$, respectively) (Table 1). Similar differences between groups were found for the HOMA-IR index (Table 1).

In this experiment, the liver histological analysis was carried out to determine the area of lipid droplets and inflammation by counting number of lymphocytes. The area of lipid droplets in the liver of obese patients without T2DM with BMI < 40 kg/m^2 significantly exceeded that one in control group ($p = 0.03$) (Table 1). The area of lipid droplets in the liver of obese patients with T2DM (with BMI < 40 kg/m^2 and BMI > 40 kg/m^2) was significantly higher than that in control group ($p < 0.001$) and obese patients without

TABLE 1. STUDIED PARAMETERS IN GROUPS

Parameters	Parameters of studies groups				
	1 Control group	2 Obese patients without type 2 diabetes with BMI < 40 kg/m²	3 Obese patients without type 2 diabetes with BMI > 40 kg/m²	4 Obese patients with type 2 diabetes with BMI < 40 kg/m²	5 Obese patients with type 2 diabetes with BMI > 40 kg/m²
Insulin (pg/ml)	45.93 (39.26-61.25)	93.42 (44.41-170.50)	134.30 (67.79-237.10) $p_1 = 0.003$	502.2 (255.70-1248.00) $p_1 < 0.001$ $p_2 = 0.01$ $p_3 = 0.004$	262.2 (134.00-530.70) $p_1 < 0.001$ $p_2 = 0.03$ $p_3 = 0.02$
glucose (mmol/l)	5.05 (5.30-5.51)	5.66 (4.87-6.48) $p_1 = 0.006$	5.14 (4.71-6.08)	6.83 (5.61-9.38) $p_1 < 0.0001$ $p_2 = 0.007$ $p_3 = 0.0002$	7.09 (5.92-9.74) $p_1 < 0.001$ $p_2 < 0.001$ $p_3 < 0.001$
hOMA-IR (c. u.)	6.15 (4.55-8.30)	13.11 (5.99-22.68)	19.68 (11.62-36.41) $p_1 < 0.001$	127.90 (48.77-292.50) $p_1 < 0.001$ $p_2 = 0.006$ $p_3 = 0.004$	52.00 (30.22-211.00) $p_1 < 0.001$ $p_2 = 0.007$ $p_3 = 0.01$ $p_4 = 0.03$
area of lipid droplets (%)	3.37 (1.84-5.26)	5.16 (2.71-26.46) $p_1 = 0.03$	4.10 (2.20-7.98)	22.24 (16.78-25.46) $p_1 < 0.001$ $p_3 < 0.001$	19.17 (11.37-32.24) $p_1 < 0.001$ $p_2 < 0.003$ $p_3 < 0.001$
lymphocyte count	–	121.00 (92.50-134.50)	75.00 (50.50-94.50) $p_2 = 0.03$	98.00 (71.00-137.00)	127.00 (102.00-163.50) $p_3 < 0.001$
sOD gene expression (c. u.)	1.01 (0.99-1.03)	0.96 (0.88-1,06)	0.92 (0.89-0.94) $p_1 = 0.001$	0.90 (0.89-1.05)	0.91 (0.88-0.96) $p_1 = 0.001$
amounts of mtDNA	3253 (2097-4280)	1412 (531-3221) $p_1 = 0.002$	711 (520-777) $p_1 < 0.0001$	1390 (818.3-2072.0) $p_1 = 0.008$ $p_3 = 0.005$	1035 (745-1566) $p_1 < 0.001$ $p_3 < 0.001$

Note. Significance determined using the nonparametric Mann–Whitney test (Mean±SD); "p_x", significant differences.

T2DM with BMI > 40 kg/m² ($p < 0.001$) (Table 1). It should be noted that the area of lipid droplets in the liver of obese patients with T2DM with a BMI < 40 kg/m² *vs* BMI > 40 kg/m² was significantly higher (Table 1). Healthy donors showed no signs of liver inflammation. The number of leukocytes in the liver of obese patients without T2DM with a BMI > 40 kg/m² *vs* BMI < 40 kg/m² was higher ($p = 0.03$). The number of leukocytes in the liver of obese patients with T2DM with BMI > 40 kg/m² *vs* BMI < 40 kg/m² was significantly higher ($p < 0.001$) (Table 1). The control group showed a normal liver structure without signs of inflammation. However, focal liver steatosis (small- and medium-droplet) and single drops were observed in some healthy donors. Small, medium, and large droplet steatosis was observed in obese patients without disturbed carbohydrate metabolism. Hepatocyte dystrophy and karyolysis was found in 40% and 17%, respectively. Intracellular cholestasis and signs of inflammation (lymphocyte infiltration) were detected in 41.6% and 58% of patients, respectively. At the same time, 30% subjects had no steatosis or single drops similar to the control group. Small, medium, and large droplet steatosis was observed in obese patients with impaired carbohydrate metabolism. Hepatocyte dystrophy was observed in almost all patients (93.75%), whereas karyolysis manifestations in lower percentage (62.5%). Intracellular cholestasis and lymphocytic infiltration were detected in 81.25% of patients. Thus, steatosis and inflammation progressed with increased BMI and developing insulin resistance.

In this study, the level of *SOD1* gene expression in the liver of obese patients with and without T2DM with BMI > 40 kg/m² was significantly lower than in healthy donors (Table 1), which indicates reduced antioxidant protection along with increased BMI. Positive correlations were found between the *SOD1*

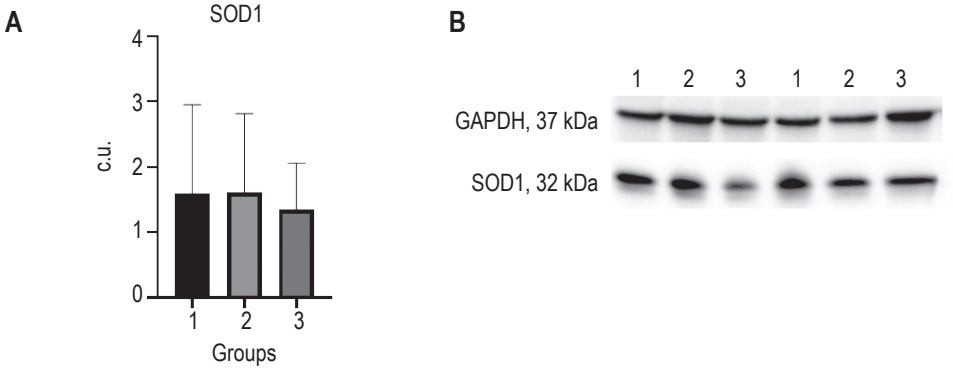

Figure 1. SOD1 protein production in the liver

Note. 1, healthy donors; 2, obese patients without T2DM; 3, obese patients with T2DM. A, production of SOD1 protein in the liver, normalized to the reference protein GAPDH in three groups. B, chemiluminescence images of SOD1 and GAPDH proteins in the liver.

expression and BMI (r = 0.74) as well as between the *SOD1* expression and mtDNA (r = 0.65) in the control group. Consequently, in normal physiological conditions in the liver, mitochondria begin to function vigorously in response to an excessive FFA intake with increased BMI. In turn, elevated β-oxidation activates the antioxidant mechanisms of the cell defense against high ROS levels, which are formed due to errors in electron transfer in the mitochondrial respiratory chain. A negative correlation between the *SOD1* expression and the index of insulin resistance HOMA-IR (r = -0.61) was found in obese patients without impaired carbohydrate metabolism. Thus, the likelihood of developing insulin resistance increases along with decreased antioxidant protection.

We also performed a semi-quantitative analysis of SOD1 protein level in the liver. Thus, the value of densitometry of the SOD1 protein relative to the reference GAPDH protein in the liver in healthy donors was 1.6±1.3 c. u., 1.6±1.2 c. u. in obese patients without T2DM and 1.5±0.9 c. u. in obese patients with T2DM (Figure 1). A negative correlation between the production of SOD1 protein and the area of lipid droplets in the liver was found in obese patients without T2DMconfirming the theory about decreased activity of the antioxidant system in obesity.

As previously mentioned, changes in mitochondrial structure and function are considered as a key hallmark of NAFLD [3] liver cancer, and indications for orthotopic liver transplantation. Given its high prevalence, the absence of FDA-approved drugs for NAFLD is noticeable. In the pathogenesis of NAFLD, it is well known that mitochondrial dysfunction arises as a result of changes in ETC complexes and the membrane potential (Δψm. The results obtained using electron microscopy showed that mitochondria were enlarged and the mitochondrial matrix contained paracrystalline inclusions in mice with altered fatty acid oxidation and hepatic steatosis [7].

MtDNA is most susceptible to ROS effects since it is located near the site of ROS production [7]. Consequently, mtDNA will be more susceptible to ROS when the activity of the antioxidant system decreases. In this experiment, the amount of mtDNA in the liver in all groups was significantly lower in comparison with healthy donors ($p < 0.05$) (Table 1). The amount of mtDNA in the liver of obese patients without T2DM with BMI > 40 kg/m^2 was significantly lower than in obese patients with T2DM with BMI < 40 kg/m^2 ($p = 0.005$) and BMI > 40 kg/m^2 ($p < 0.001$) (Table 1). A negative correlation between the amount of mtDNA and the area of lipid droplets in the liver was found in healthy donors (r = -0.71) and obese patients without impaired carbohydrate metabolism (r = -0.46). This proves that in normal physiological conditions, the amount of mtDNA increases along with increasing steatosis to compensate for excess FFA levels. However, this process is disrupted in obesity. A negative correlation between the amount of mtDNA in the liver and the plasma insulin level (r = -0.53) and the insulin resistance index HOMA-IR (r = -0.54) was found in obese patients with T2DM. A decrease in the amount of mtDNA in the liver may lead to the development of T2DM.

Thus, a decrease in liver antioxidant defense in obese patients leads to mitochondrial vulnerability, which contributes to steatosis progression.

Conclusion

1) The expression *SOD1* and the number of mtDNA copies in the liver of obese patients with and without T2DM with BMI > 40 kg/m^2 is lower than in healthy donors.

2) The SOD1 protein level and the number of mtDNA copies are interrelated and negatively correlate with the area of lipid droplets in the liver of obese patients without T2DM.

3) The number of mtDNA copies is negatively associated with the plasma insulin level and HOMA-IR index in patients with T2DM.

4) A decrease in antioxidant protection in the liver leads to the vulnerability of mitochondria in obese patients, contributing to the progression of steatosis and insulin resistance.

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Авторы:

Комар А.А. *— аспирант Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Шункина (Скуратовская) Д.А. *— к.б.н., старший научный сотрудник Центра иммунологии и клеточных, биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Вульф М.А. *— к.б.н., старший научный сотрудник Центра иммунологии и клеточных технологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Ву Хунг Куанг *— аспирант Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Тодосенко Н.М. *— к.б.н., старший научный сотрудник Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Затолокин П.А. *— к.м.н., старший научный сотрудник Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Кириенкова Е.В. *— д.м.н., старший научный сотрудник Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Газатова Н.Д. *— к.б.н., старший научный сотрудник Центра иммунологии и клеточных, биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Литвинова Л.С. *— д.м.н., директор Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Authors:

Komar A.A., *Postgraduate Student, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Shunkina (Skuratovsvkaia) D.A., *PhD (Biology), Senior Research Associate, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University Kaliningrad, Russian Federation*

Vulf M.A., *PhD (Biology), Senior Research Associate, Center for Immunology and Cellular Biotechnology at the Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Vu Hung Quang, *Postgraduate Student, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Todosenko N.M, *PhD (Biology), Senior Research Associate, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Zatolokin P.A., *PhD (Medicine), Senior Researcher at the Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Kirienkova E.V., *PhD, MD (Medicine), Senior Research Associate, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Gazatova N.D., *PhD (Biology), Senior Research Associate, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Litvinova L.S., *PhD, MD (Medicine), Director, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

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