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ORIGINAL ARTICLE

INFLUENCE OF INDUCED DIABETES MELLITUS ON HORMONAL PROFILE OF LEWIS LUNG CARCINOMA IN BALB/C NUDE MICE

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ABSTRACT

Purpose of the study. The assessment of diabetes mellitus (DM) effect on levels of sex hormones in tumor and peritumoral tissues in BALB/c Nude mice with Lewis lung carcinoma (LLC).
Materials and methods. The study included 42 male and female BALB/c Nude mice aged 8–9 weeks weighing 21–22 g. Alloxan-induced DM was reproduced in mice of the main group, and then LLC was transplanted. Levels of estrone (E1), estradiol (E2), testosterone (T), progesterone (P4) and prolactin (PRL), as well as steroid hormone receptors: estrogens (REα, REβ), androgens (RA), and progesterone (RP4) were measured by RIA and ELISA in samples of tumor and peritumoral tissues. Animals with LLC without DM were used as controls. The statistical analysis was performed using the Statistica 10 program; differences were considered significant at $p < 0.05$.
Results. DM in males was reproduced only after a double injection of alloxan, and was characterized by lower blood glucose levels compared to females. The growth of LLC in animals with alloxan-induced DM was possible only in female BALB/c Nude mice; in BALB/c Nude males, the tumor could not be transplanted either independently or in combination with DM. Females in the main group showed greater average tumor volumes throughout the experiment and reduced survival, compared to the control group. Tumor samples from females with LLC+DM were more saturated with sex steroids, but depleted in steroid hormone receptors, which probably contributed to the ability to avoid the body's regulatory signals.
Conclusion. The growth of LLC in presence of induced DM was sex-dependent, since the tumor could not be transplanted to male mice. DM affected the levels of sex steroids and their receptors tumor tissues in female BALB/c Nude mice.

Keywords:
diabetes mellitus, Lewis lung carcinoma, BALB/c Nude mice, sex steroids, sex steroid receptors

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ВЛИЯНИЕ ИНДУЦИРОВАННОГО САХАРНОГО ДИАБЕТА НА ГОРМОНАЛЬНЫЙ ФОН КАРЦИНОМЫ ЛЬЮИСА У МЫШЕЙ ЛИНИИ BALB/C NUDE

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РЕЗЮМЕ

Цель исследования. Изучение влияния сахарного диабета (СД) на содержание половых гормонов в опухоли и перифокальной зоне у мышей BALB/c Nude с карциномой Льюиса.

Материалы и методы. В работе использовали 42 мыши линии BALB/c Nude обоего пола, 8–9 недельного возраста с массой тела 21–22 г. У мышей основной группы с помощью инъекций аллоксана индуцировали СД, на фоне которого перевивали карциному Льюиса (LLC). В образцах опухолей и их перифокальных зон радиоиммунным методом (РИА) и иммуноферментным методом (ИФА) определяли уровень эстрона (Е1), эстрадиола (Е2), тестостерона (Т), прогестерона (Р4) и пролактина (ПРЛ), а также рецепторов стероидных гормонов: эстрогенов (REα, REβ), андрогенов (RA), и прогестерона (RP4). В качестве контроля изучали животных с самостоятельным ростом LLC. Статистический анализ проводили с использованием программы Statistica 10, значение $p < 0,05$ рассматривалось как показатель статистической значимости.

Результаты. Сахарный диабет у самцов воспроизводился только после двухкратного введения аллоксана и характеризовался более низкими показателями глюкозы крови, по сравнению с самками. Рост карциномы Льюиса на фоне индуцированного аллоксаном сахарного диабета оказался возможным только у самок мышей линии BALB/c Nude, у самцов линии BALB/c Nude опухоль не перевивалась ни в самостоятельном, ни в сочетанном с СД вариантах. У самок основной группы установлены большие средние объемы опухолей на протяжении всего эксперимента и сокращение продолжительности жизни, по сравнению с группой контроля. При этом, образцы опухоли у самок с развитием злокачественного процесса на фоне СД хотя и были более насыщены половыми стероидами, оказались обеднены рецепторами стероидных гормонов, что, вероятно, способствовало возможности избегать регуляторных сигналов организма.

Заключение. Рост карциномы Льюиса на фоне индуцированного СД имел половую зависимость, опухоль не перевивалась самцам мышей. СД оказал влияние на уровень половых стероидов и их рецепторов в злокачественной опухоли у самок мышей BALB/c Nude.

Ключевые слова:
сахарный диабет, карцинома Льюиса, мыши линий BALB/c Nude, половые стероиды, рецепторы половых стероидов

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INTRODUCTION

The interaction between diseases was recognized as a key factor influencing the natural course of diseases, including the development of the malignant process [1; 2]. Synergetic relationships between diseases co-existing in the population can influence the dynamics of the epidemic, which leads to noticeable differences in health outcomes compared to the disease occurring in isolation [3]. The concept of disease interaction in the epidemiology of diabetes mellitus (DM) is well documented both at the population and individual level. There is convincing evidence of an association between DM and other macro- and microvascular diseases, such as hypertension, coronary heart disease and congestive heart failure, as well as immunodeficiency [4; 5].

Other studies have also shown a significant association between DM and several oncological diseases, such as colorectal cancer, pancreatic cancer, endometrial and ovarian cancer, stomach, kidney and thyroid cancer, as well as leukemia [6]. Moreover, cancer patients with diabetes mellitus or with abnormal plasma glucose levels have a more unfavorable prognosis. In malignant cells that are exposed to excess physiological glucose concentrations, a change in intracellular signaling is detected, which leads to more aggressive phenotypes [7].

The mechanisms underlying the high aggressiveness of glucose-induced cancer are different for each type of cancer. Glucose can activate many signaling pathways, for example, ERK, STAT3 and NsF-κB, including cell proliferation, metastatic activity and chemoresistance of cancer cells. Activation of these intracellular pathways regulates the transcription of their specific downstream target genes, which contribute to the development of aggressive phenotypes. In addition, it was found that the long-term clinical outcome and survival are worse in cancer patients with diabetes mellitus, whose plasma glucose levels are poorly controlled [8]. Therefore, high glucose content has been proposed and identified as a mechanism by which diabetes mellitus is associated with cancer progression [9].

The purpose of this study was to study the effect of diabetes mellitus on the content of sex hormones in the tumor and perifocal zone in BALB/c Nude mice with Lewis carcinoma.

MATERIALS AND METHODS

Experimental studies were carried out on 42 mice of both sexes of the BALB/c Nude lines, 8–9 weeks of age with a body weight of 21–22 g. Mice of the BALB/c Nude lines were purchased at the Laboratory Animal Nursery in Pushchino, Russian Federation. The animals were kept in an environment free of specific pathogens (SPF), with a 12-hour light/dark cycle. The choice of BALB/c Nude mice for this study is associated with defects in the immune system caused by the absence of a thymus gland and a deficiency of T cells [10], thanks to which the introduction of alloxan in experimental animals was able to induce diabetes mellitus and cure Lewis carcinoma.

All mice were kept in autoclave micro-insulator cages equipped with sterilized pine wood chips at a constant (24 h) temperature (22 °C) and humidity (40–70 %). Throughout the experiment, the mice were fed sterilized food and water. All manipulations were carried out in sterile conditions at a laminar flow workstation. All studies were conducted in accordance with the requirements and conditions set out in the "International Recommendations for conducting Biomedical research using animals" and the Order of the Ministry of Health of the Russian Federation No. 267 dated 06/19/03 "On approval of the rules of laboratory practice". Work with animals was carried out in accordance with the rules of the "European Convention for the Protection of Animals Used in Experiments" (Directive 86/609/EEC). Protocol of the Ethics Committee No. 7/111 of 02/26/2021.

The females of the BALB/c Nude lines were divided into the following groups: the control group – mice with Lewis carcinoma (LLC) (n = 14) and the main group of mice with Lewis carcinoma on the background of DM (n = 14). Of these, 7 animals with independent growth LLC and 7 animals with LLC+The dynamics of tumor growth and life expectancy were observed, and the remaining animals were guillotined 19 days after the tumor was transplanted in order to study sex hormones and their receptors in tissues.

Males were also divided into groups of 7 animals: mice that were transplanted with Lewis carcinoma in an independent variant; mice that were transplanted with Lewis carcinoma on the background of DM.

Diabetes was reproduced in females by a single intraperitoneal injection of alloxan at a dose of 350

mg/kg; in males – by a double intraperitoneal injection of alloxan at a dose of 350 mg/kg.

To transplant Lewis carcinoma in an independent version, 0.5 ml of LLC tumor suspension containing 0.5 million tumor cells was injected under the skin of the back just below the right shoulder blade. Animals of the main groups, for the development of the tumor process against the background of DM, the tumor was transplanted in a similar independent way: females on the 5th day after the introduction of alloxan and a steady increase in blood glucose levels, males on the 12th day from the first injection of alloxan. Measurements of tumor nodes were carried out in 3 dimensions, the volume of the tumor was calculated using the formula (R1 + R2 + R3) [10]. In groups with tumor grafting to study the life expectancy of animals, tumor measurements were carried out weekly until the death of animals. To determine hormones and their receptors, tumor samples, their perifocal zones, as well as the pancreas were taken on ice. 1 % cytosolic fractions prepared on 0.1M potassium phosphate buffer pH 7.4 containing 0.1 % Twin-20 and 1 % BSA were obtained from the tissues. The level of estrone (E1), estradiol (E2), testosterone (T), progesterone (P4), prolactin (PRL), as well as the content of insulin and C-peptide were determined by RIA (Immunotech, Czech Republic), the concentration of steroid hormone receptors: estrogens REa and REß, androgen receptors RA and progesterone RP4 were determined The ELISA method (Cloud-Clone Corp. China), blood glucose by biochemical method (Olveix Diagnosticum),

Statistical processing of the results was carried out using the Statistica 10.0 program. The data are presented as an average value ± standard error of the average. The correspondence of the distribution to the normal was evaluated using the Shapiro-Wilk criterion. The significance of the differences between independent samples was assessed using the Student's t-test and the Mann-Whitney test ($p < 0.05$).

RESEARCH RESULTS

First of all, we studied the development of diabetes mellitus in mice of different sexes. It was found that in all female mice on the 5th day after the introduction of alloxan, the blood glucose level was 26.94 ± 1.2 mM/L versus 5.8 ± 0.7 in intact animals and remained at this level with slight fluctuations throughout the entire duration of the experiment until the death of the animals (Table 1).

At autopsy in females with diabetes macroscopically: the kidneys are enlarged, the pancreas is almost 2 times smaller than in intact animals, it looks "mucous". The level of insulin and C peptide in the pancreas in the females of the main group was 5.4 times and 1.6 times higher, respectively (44.2 ± 3.8 mcIU/g of tissue and 2.95 ± 3.1 pm/g of tissue, respectively, in the main group versus 8.15 ± 0.8 mcIU/g of tissue and 1.86 ± 0.17 pm/g of tissue in intact animals), which indicates the development of insulin resistance in these animals.

The results of measurements of average tumor volumes in female mice with and without diabetes mellitus are presented in the table 1.

Table 1. Lewis carcinoma volume and blood glucose levels in female mice

Days after starting the experiment	8 Days	11 Days	15 Days	19 Days	22 Days
Tumor V cm^3 Main group	0.36 ± 0.018*	4.07 ± 0.13*	7.76 ± 0.18*	10.32 ± 0.4*	-
Blood glucose (mM/L) in the main group	26.91 ± 0.56*	26.41 ± 0.59*	26.36 ± 0.81*	26.48 ± 0.69*	-
Tumor V cm^3 in the control group	0.1 ± 0.011	0.31 ± 0.012	0.94 ± 0.07	2.98 ± 0.15	4.71 ± 0.14
Blood glucose (mM/L) in the control group	5.78 ± 0.12	5.36 ± 0.17	5.63 ± 0.11	5.9 ± 0.12	5.63 ± 0.14

Note: * – statistically significant differences in comparison with the control group, $p < 0.05$.

It is obvious that in the group of female mice with Lewis carcinoma, reproduced against the background of diabetes mellitus, the tumor developed more intensively: on day 8 it was 3.6 times larger than in animals of the control group, on day 11 – almost 13 times, on day 15–8.3 times and before the death of mice on day 19–3.5 times. The greatest growth of the tumor occurred in the period of 11–15 days. The life expectancy of mice with Lewis carcinoma on the background of diabetes mellitus was 19–20 days, whereas with isolated Lewis carcinoma – 28–29 days ($p < 0.05$).

In all male mice, after 1 administration of alloxan, the glucose level didn't significantly rise, so we performed 2 injections at the same dose 8 days after the 1st one. The glucose level is shown in the table 2.

The next day after repeated administration of alloxan, the skin of all mice acquired a bluish hue. Blood for measuring glucose levels was taken with difficulty. Lewis carcinoma was transferred to male mice on day 12 from the 1st administration of alloxan and on day 4 from the repeated administration of alloxan. 4 days after the transfer of the tumor suspension, white spots with a diameter of about 5 mm without signs of tumor growth were observed at the injection site. All the mice had dry atrophic skin. No tumors were detected 30 days after the transplant.

Thus, female mice were more susceptible to the reproduction of diabetes mellitus and Lewis tumors

Table 2. Blood glucose levels in male mice with alloxan-induced diabetes

Days after starting the experiment	Inital	7 Days	8 Days	9 Days	12–19 Days
Glucose levels in DM group (mM/L)	6.6 ± 0.12	7.80 ± 0.11*	9.2 ± 0.23*	9.47 ± 0.12*	14.46 ± 0.21*

Note: * – statistically significant differences in comparison with the initial levels, $p < 0.05$.

Table 3. The content of hormones and receptors in the tumor and its perifocal zone during various processes in female mice

Indicators	Tumor		Perifocal zone	
	LLC	DM + LLC	LLC	DM + LLC
E1 (pg/t)	47.7 ± 2.39**	101.8 ± 2.3*	517.0 ± 2.8	97.0 ± 2.14*
E2 (pg/g t)	62.3 ± 1.37**	84.7 ± 2.62*,**	127.3 ± 1.44	55.5 ± 1.46*
T total (ng/g t)	0.21 ± 0.02**	0.7 ± 0.06*,**	1.0 ± 0.076	0.2 ± 0.01*
P4 (ng/g t)	1.5 ± 0.064**	5.0 ± 0.38*,**	3.7 ± 0.06	3.8 ± 0.177
PRL (ng/g t)	3.0 ± 0.306**	13.2 ± 0.28*,**	12.5 ± 0.42	34.9 ± 1.33*
REα (ng/g t)	2.2 ± 0.099**	1.2 ± 0.11*,**	10.3 ± 0.33	6.6 ± 0.3*
REβ (ng/g t)	4.6 ± 0.05**	2.9 ± 0.25*,**	12.3 ± 0.4	7.4 ± 0.25*
RA (ng/g t)	0.33 ± 0.008**	0.3 ± 0.0056**	2.5 ± 0.06	1.4 ± 0.10*
RP4 (ng/g t)	0.33 ± 0.02**	0.21 ± 0.009*,**	3.7 ± 0.076	1.4 ± 0.11*

Note: statistically significant differences in comparison with: * – the respective samples in the control group; ** – perifocal zone of the entire group ($p < 0.05$).

in them, and Lewis carcinoma on the background of diabetes mellitus grew more intensively. The males turned out to be quite resistant to the reproduction of diabetes mellitus and not at all susceptible to transplantation of Lewis carcinoma, either in an independent variant or against the background of diabetes mellitus.

The question arose: is this related to the level of sex hormones and, especially, to the activation of tumor growth under the influence of sex hormones?

Thus, we studied the level of sex hormones and their receptors in the tumor tissue of female mice with various growth variants, as well as in the tissue surrounding the tumor, I.e. the perifocal zone.

It was found that the tumor tissue growing against the background of diabetes mellitus contained more estrogens: E1–2.1 times and E2–1.4 times relative to the tumor tissue growing in an independent variant (Table 3). At the same time, the level of these hormones in the perifocal zone was lower than in the corresponding samples with independent growth of Lewis carcinoma: E1–5.3 times and E2–2.3 times. The T content in the tumor tissue during its growth against the background of diabetes mellitus turned out to be 3.3 times higher, and in its perifocal zone 5 times lower, compared with similar samples of the control group. In the tumor tissue growing against the background of diabetes mellitus, the level of P4 and PRL was increased by 3.3 times and 4.4 times, respectively, in the tissue of its perifocal zone, only the level of PRL was increased by 2.8 times, while P4 had no significant differences from the corresponding region with independent growth of Lewis carcinoma.

The content of estrogen and progesterone receptors in the females of the main group was reduced in the tumor tissue and its perifocal zone: REα – by 1.8 times and 1.6 times, respectively, REβ – by an average of 1.6 times and RP4 – by 1.5 and 2.6 times, respectively, relative to the indicators in the animals of the control group. The androgen receptor in the tumor tissue had no significant differences between the indicators on the background of diabetes mellitus and without it, and in the tissue of the perifocal zone of the tumor in the animals of the main group was reduced by 1.8 times. It should be noted that, despite the decrease in the level of sex hormone receptors in the tissue of the perifocal zone of the tumor in diabetes mellitus, the indicators remained significantly higher than their level in the tumor tissue.

DISCUSSION

On the background of the ongoing epidemic of both obesity and diabetes, there is great interest in understanding the impact of these conditions on a wide range of cancers. DM is known to be associated with an increased risk of breast cancer, colorectal cancer, endometrial cancer, pancreatic cancer, liver and bladder cancer, but not prostate cancer [11]. In our study, it was shown that in male mice of the BALB/c Nude line, unlike females, it was possible with the help of alloxan injections to cause diabetes at a later date and with lower blood glucose levels. In males, it was not possible to transfer Lewis carcinoma either in an independent version or against the background of diabetes mellitus, which we associate with the protective role of the hormonal background, in particular androgens.

At the same time, it was found that throughout the experiment, in females with an increase in Lewis carcinoma on the background of DM, the blood glucose level was more than 4 times higher than in animals of the control group. At the same time, a malignant tumor on the background of DM developed much faster than in an independent variant, the volume of tumors increased rapidly, the life expectancy of females was less. Experimental studies of gestational diabetes have shown that in response to an intrauterine environment with a high glucose content, the fetus undergoes a number of adaptive changes, such as acceleration of catabolism and glucose utilization, which affects its growth and development [12]. Drawing a certain parallel between the growth of a malignant tumor and pregnancy, when both physiological and pathological processes are "protecting someone else's in their own", it can be assumed that a malignant tumor, receiving additional glucose resources, could significantly accelerate its proliferative potential.

However, there is a growing understanding that the direct contribution of glucose to the metabolism of cancer cells may be greater than Warburg assumed. The effect of diabetes on cancer development is associated with complex biology, including not only insulin resistance and elevated glucose levels, but also inflammation, effects on immunity and hormonal background [11].

Sex hormones are naturally produced in the body and are of fundamental importance for controlling

functions as the oldest growth factors and as bioactive substances capable of exerting genomic effects by binding directly to nuclear receptors. Steroid hormones can also perform non-genomic functions by binding to or near the plasma membrane, causing rapid changes in cellular physiology [13]. Their production is finely regulated, because even a small change in their quantity can cause serious consequences for the whole organism [14]. Among the many functions performed by hormones, some are also associated with cell proliferation and may affect the development of cancer [15].

In our study, it was found that the tumor samples in the animals of the main group contained much higher concentrations of all steroid hormones – E2, E1, T and P4, as well as prolactin. It is obvious that in addition to high glucose concentrations, sex steroids, as well as prolactin, which can act as a growth factor, stress hormone and influence the immune system by suppressing the production of interleukin-6, were necessary for accelerated proliferation of tumor tissue. At the same time, attention is drawn to the fact that if in animals of the control group a higher content of sex steroids was found in the perifocal zone, then in animals of the main group, on the contrary, directly in the neoplasm.

The fact that we found an increase in the local content of sex hormones in the females of the main group is not unexpected. Estradiol levels are known to have been elevated in menopausal women with DM-2, suggesting that excess estrogen may also have played a role in the risk of developing insulin resistance. The link between excess testosterone and diabetes in women has been known for almost a century. In postmenopausal women, higher plasma levels of estradiol and testosterone were associated with an increased risk of diabetes mellitus [16]. In women, hyperandrogenic conditions, such as polycystic ovary syndrome, are associated with insulin resistance, glucose intolerance and subsequent diabetes mellitus. High testosterone levels cause insulin resistance due to a decrease in insulin-stimulated glucose uptake in healthy pre- and postmenopausal women [17; 18]. That is, insulin resistance has a pronounced relationship with hormonal background.

It is known that sex hormone receptors, such as androgen receptors (RA), estrogen receptors (RE) (for example, REα, REß) and progesterone receptors (RP), are a group of steroid receptors that are activated by binding ligands, androgens, estrogens and progestogens, respectively. Recent results indicate the vital role of sex hormone receptor signals in the pathogenesis of urothelial cancer, which may be the main cause of sex differences in bladder cancer. In particular, RA activation has been implicated in urothelial oncogenesis, whereas there are conflicting results regarding the effects of estrogen, which may depend on the functional activity of REα compared to REß in malignant cells [19].

It is also known that REα, REβ and RA are important receptors involved in glucose metabolism in peripheral tissues. They promote glucose and energy homeostasis during androgen/estrogen binding in these tissues by reducing lipogenesis and increasing insulin secretion and sensitivity [20].

It was interesting to find a lower content of steroid hormone receptors both in the tumor samples and in the perifocal zone in the females of the main group, compared with the control, despite an increase in the concentrations of sex steroids. This can be attributed, on the one hand, to the predominance of rapid non-genomic reactions of sex steroids, which stimulate tissue proliferation, and on the other hand, to the departure of the tumor from organizational control by regulatory authorities. Thus, it is known that triple-negative breast cancer, characterized by the complete absence of steroid hormone receptors in the tumor tissue, is a more aggressive biological subtype, unlike luminal BC [21; 22].

CONCLUSION

Thus, in our study it was shown that the growth of Lewis carcinoma against the background of alloxan-induced diabetes mellitus was possible exclusively in female mice of the BALB/c Nude line and was characterized by a large average volume of tumors throughout the experiment and a reduction in the life expectancy of animals. At the same time, tumors in females with the development of a malignant process on the background of diabetes, although they were more saturated with sex steroids, were depleted of steroid hormone receptors, which probably contributed to the possibility of avoiding regulatory signals of the body.

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