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ORIGINAL ARTICLE

ABOUT THE BLOOD CHARACTERISTICS AND ADAPTATION STATUS VARIABILITY IN INTACT BALB/C MICE OF DIFFERENT SEX

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ABSTRACT

Purpose of the study. Was to study the values and variability of traditionally determined blood parameters and index of the adaption status in intact mature Balb/c mice of different sex.
Materials and methods. Studies were carried out on 20 animals of mature age with spf-status, males (10) and females (10). Cytological and biochemical parameters of blood and weight characteristics of the organs of the immune system and adrenal glands were studied (considering the constitutional features of mice of this line). Statistica 10.0 software package was used for statistical analysis. The coefficient of variation (CV) was determined. The significance of statistical differences was assessed using the Mann-Whitney test.
Results. Sex differences were found in the ratio of albumins and globulins, the content of urea and alkaline phosphatase, the relative proportion of lymphocytes and monocytes in the blood count, the erythrocytes' count and the level of hemoglobin in erythrocytes. There were also indicators which had values of severe variability (CV up to 51 %), the number of those in males was higher than in females. The information content of the weight characteristics of the studied organs is reduced due to the constitutional features of Balb/c females. The identified sex differences indicated a higher adaptive status of female rodents compared to males and let to propose the prevalence of different activity of T-cell, B-cell and myeloid line in animals of different sexes.
Conclusion. The study of weak and moderate shifts in traditional laboratory parameters reflecting the adaptive status and characteristics of the blood of sexually mature males and females of the Balb/c line under physiological conditions made it possible to identify the sex characteristics of systemic regulatory processes that may be important for the body's resistance to malignant growth and the effectiveness of antitumor treatment. The current areas of further research are also indicated.

Keywords: individual and sex differences, adaptation status, general nonspecific adaptational reactions of the body, hematological parameters, immune processes

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Compliance with ethical standards: work with animals was carried out in accordance with the rules of the «European Convention for the Protection of Animals Used for Experimental and other Scientific Purposes» (Directive 2010/63/EU), as well as in compliance with the «International Recommendations for Biomedical Research Using Animals» and Order of the Ministry of Health of Russia No. 267 of June 19, 2003 «On Approval of the Rules of Laboratory Practice». The study was approved by the Ethics Committee of the National Medical Research Centre for Oncology (Protocol No. 11/115 of 03/01/2021).

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ОРИГИНАЛЬНАЯ СТАТЬЯ

О ВАРИАБЕЛЬНОСТИ ПОКАЗАТЕЛЕЙ КРОВИ И АДАПТАЦИОННОГО СТАТУСА ИНТАКТНЫХ МЫШЕЙ ЛИНИИ BALB/C РАЗНОГО ПОЛА

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РЕЗЮМЕ

Цель исследования. Изучение величины и вариабельности традиционно определяемых показателей крови и некоторых показателей адаптационного статуса у интактных половозрелых мышей линии Balb/c разного пола.
Материалы и методы. Исследования проведены на 20 половозрелых животных SPF-статуса, самцах (10) и самках (10). Были изучены цитологические и биохимические показатели крови и весовые характеристики органов иммунной системы и надпочечников (с учетом конституциональных особенностей мышей данной линии). При статистическом анализе использовали пакет программ Statistica 10.0. Определяли коэффициент вариации (CV). Значимость статистических различий оценивали с помощью критерия Манна-Уитни.
Результаты. Были выявлены половые различия по соотношению уровней альбумина и глобулина, содержанию мочевины и щелочной фосфатазы, относительному числу лимфоцитов и моноцитов в крови, количеству эритроцитов и содержанию гемоглобина в эритроцитах. Также были отмечены показатели, отличавшиеся сильной вариабельностью (CV до 51 %), число которых у самцов было большим, чем у самок. Информативность весовых характеристик исследованных органов была снижена вследствие конституциональных особенностей самок линии Balb/c. Результаты анализа показателей указывали на более высокий адаптационный статус самок по сравнению с самцами и позволяли предположить различную активность Т-клеточных, В-клеточных и миелоидных звеньев иммунитета у животных разного пола.
Заключение. Изучение слабых и умеренных сдвигов традиционных лабораторных показателей, отражающих адаптационный статус и характеристики крови половозрелых самцов и самок линии Balb/c в условиях физиологической нормы, позволило выявить половые особенности системных регуляторных процессов, которые могут иметь значение для устойчивости организма к злокачественный росту и эффективности противоопухолевых воздействий. Указаны актуальные направления дальнейших исследований.

Ключевые слова: индивидуальные и половые отличия, адаптационный статус, общие неспецифические адаптационные реакции организма, гематологические показатели, иммунные процессы

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Соблюдение этических стандартов: работу с животными проводили в соответствии с правилами «Европейской конвенции о защите животных, используемых в экспериментах» (Директива 2010/63/EU), а также в соответствии с «Международным рекомендациям по проведению медико-биологических исследований с использованием животных» и Приказом Минздрава России от 19 июня 2003 г. № 267 «Об утверждении правил лабораторной практики». Исследование одобрено этическим комитетом ФГБУ «НМИЦ онкологии» Минздрава России (протокол № 11/115 от 01.03.2021 г.).

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INTRODUCTION

Currently, in experimental oncology, as in other medical sciences, linear animals are widely used to standardize the results of research and preclinical trials of new therapeutic agents and technologies. At the same time, the genetic proximity of the objects of study helps to reduce the variability of changes caused by the development of tumors and the action of antitumor factors, but still cannot completely neutralize it. This is indicated by information about the characteristics of certain lines of experimental animals, which may manifest themselves to different degrees in different individuals [1; 2]. In addition, in mongrel animals and laboratory rodents of some lines, the dependence of several indicators, both under normal conditions and in the malignant process, on age [3; 4] and gender [5; 6] was noted.

At the present stage, when conducting experiments *in vivo*, in most cases it is customary to pay attention, first, to sharp changes in laboratory parameters [7]. In this regard, the question of the severity of individual and sexual differences and the factors that cause the heterogeneity of the condition in physiological conditions and pathology for animals of many widely used lines remains insufficiently studied [2; 4]. Meanwhile, individual and gender differences in the state of regulatory systems and the sensitivity of the body to the action of various antitumor agents and accompanying therapy factors, determining the adaptive status of humans and animals, can cause noticeable variations in the dynamics of the malignant process and the effectiveness of complex antitumor treatment [2; 8; 9]. At the same time, it should be borne in mind that modern means of traditional antitumor treatment, in addition to the direct damaging effect on the tumor, have a systemic effect on the body, thereby modulating their own direct effects on malignized cells. Thus, clarification of the issue of individual and sexual differences in adaptive status is necessary for the correct interpretation of research results in conditions of malignant growth, especially when the malignant process and common comorbid pathologies are combined. In addition, the assessment of the heterogeneity of the condition of animals will allow us to determine approaches to optimizing antitumor treatment and accelerate the search for effective, pathogenetically justified antitumor agents.

As an object of research of this kind, mice of the Balb/c line are of interest, belonging to the "old" at the time of creation and the most widely used lines of laboratory animals [1], which also gave rise to the first line of immunodeficient mice (Balb/c nude) capable of supporting the growth of human malignant tumors [10; 11]. As is known, Balb/c mice are distinguished by a good ability to learn, reproduce and feed offspring, as well as low aggressiveness and the highest brain weight ratio compared to this indicator in mice of other lines. At the same time, animals of this line are characterized by high emotionality and low stress resistance, high sensitivity to the action of ionizing radiation, the carcinogenic effect of certain substances, gastrointestinal infections, susceptibility to diseases of the cardiovascular system, the development of amyloidosis of the spleen, etc. [1]. Thus, the characteristic features of Balb/c mice, manifested in different individuals to varying degrees, create the basis for the heterogeneity of the functional state of these laboratory animals and, therefore, for variations during the pathological process and the body's responses to therapeutic effects. Meanwhile, there is no information in the literature on a comprehensive and consistent study of individual differences in the functional state of Balb/c mice under physiological norm conditions.

The heterogeneity of the state of laboratory animals, as a rule, is reflected, somewhat more or less, in the level of blood characteristics and some other simple system parameters that can be used to objectify research results. This determines the expediency of evaluating variations of such indicators in linear animals in physiological and pathological conditions. Although this problem is broader than the question of the relationship of functional characteristics with the gender of laboratory rodents, nevertheless, when studying the heterogeneity of the initial state of Balb/c mice, the analysis of changes in blood parameters and other parameters should be carried out considering the sex of these animals as the most obvious constitutional difference between individuals of the same line.

The purpose of the study was to study the magnitude and variability of traditionally determined blood parameters and some indicators of adaptive status in intact sexually mature Balb/c mice of different sexes.

MATERIALS AND METHODS

The studies were carried out on 20 intact sexually mature mice of the Balb/c line of the vivarium of the National Medical Research Centre for Oncology. The initial batch of animals was obtained in the nursery "Rappolovo". Prior to inclusion in the study, the animals were kept in an SPF-status vivarium. The weight of males (*n* = 10) ranged from 22.5 – 30 g, the weight of females (*n* = 10) ranged from 27.5 – 34 g. This corresponded to the age of 9–11 weeks in males and the age of 14–16 weeks in females [12]. The specified age difference between animals of different sexes was random and was due to the restriction of the possibility of choosing animals of different sexes that exactly match in age. Thus, in general, taking into account sexual dimorphism, the age difference between males and females for individual individuals could be from 3 to 7 weeks. According to the established standards, the life span and habitat conditions of the studied Balb/c mice should be considered as SPF-status animals at the age corresponding to the first half of the reproductive period [12–14]. During the experiments, the international rules of bioethics were observed.

As the studied indicators, the indicators of general and biochemical blood analysis determined by instrumental methods, as well as the weight and weight coefficients of the immune system organs (thymus, spleen) and adrenal glands characterizing the adaptive status of animals were taken [15; 16]. The animals were euthanized by decapitation. Necropsy, isolation and weighing of organs were performed. To determine the characteristics of the blood obtained after euthanasia, the Exigo EOS vet hemoanalyzer (Boule Medical A. B., Sweden) and the VetScanVS2 biochemical analyzer (ABAXIS Inc., Germany) were used.

Statistical processing of the results of the study was carried out using the software package “Statistica 10”. The range of variations of the studied indicators, their medians, averages and errors of averages, as well as the coefficient of variation (CV) were determined. The nonparametric Mann-Whitney criterion was used to evaluate the differences in the variation series.

STUDY RESULTS

Analysis of the studied parameters in intact Balb/c SPF-status mice at the age corresponding to the first half of the reproductive period revealed a number of differences related to the sex of the animals. At the same time, peculiarities in the variability of the values of the studied blood parameters and characteristics of the adaptive status in males and females were also noted (Tables 1–3).

Differences in the characteristics of the red blood germ in mice of different sexes were associated with the peculiarities of the distribution of hemoglobin (Table 1). The level of red blood cells in the blood of females statistically significantly exceeded this indicator in males by 23 %. At the same time, the average hemoglobin content in the red blood cells of males was slightly higher than that of females, so that the levels of hemoglobin in the blood as a whole in animals of different sexes did not statistically differ. At the same time, most of the characteristics of the red blood germ showed an average variability of values in animals of both sexes (from 10 to 20 %, Table 1).

More pronounced sex differences were noted for the white blood parameters of Balb/c mice (Table 1). Thus, females had noticeably higher (1.2 times) values of the relative number of lymphocytes and significantly lower (almost 2 times) values of the relative number of monocytes than males. At the same time, the percentage of lymphocytes in the group of females was surprisingly stable (CM did not exceed 5 %), while the total number of leukocytes in these animals, on the contrary, was characterized by strong variability (CM more than 40 %). In males, in contrast to females, the most variable indicator was the relative number of monocytes (CV more than 37 %).

The level of platelets in the blood of animals of different sexes was similar. At the same time, a strong variability of this indicator (CV more than 36 %) was noted in females (Table 1).

Table 2 provides information on the biochemical blood parameters available for instrumental determination of Balb/c mice of different sexes. As can be seen from the table, there was a tendency for females to slightly increase the total protein content compared to that noted in males. At the same time, the compared groups of animals did not differ statistically significantly in the content of globulins in the blood. The level of albumins in the blood of females was almost 1.5 times higher than this indicator in males, which caused a pronounced difference between individuals of different sexes also in terms of the albumin-globulin index (1.6 times). In turn, male mice had higher levels

of alkaline phosphatase and urea than females (1.5 and 1.4 times, respectively) (Table 2). It should be noted that the values of most biochemical parameters determined in the blood of males were characterized by strong variability (CV from 22.6 to 43.8 %), whereas in females the lower limit of CV values corresponding to a strong variability of indicators (20 %) was overcome only for the content of alanine aminotransferase and albumin-globulin index (Table 2).

Table 3 provides information on the weight and weight coefficients of the immune system and adrenal glands. As already noted, females were characterized by greater weight than males, which indicated a difference in the age of the animals of the compared groups. At the same time, the weight of females in the group was characterized by low variability (CV less than 7 %). Attention was drawn to a more significant mass of all the studied organs of females compared with these indicators in males (differences of 1.5, 2 and 1.8 times, respectively, for the thymus, adrenal glands and spleen). At the level of the weight coefficients of the thymus, this difference was leveled due to the higher weight of the females. The values of the thymus-adrenal mass ratio had no sex differences.

The weight parameters of the thymus (the mass of the organ and its weight coefficient) were characterized by strong variability in animals of both sexes (CV 32.7–41.7 %). In males, the weight indices of the spleen also differed by very strong variability (CV up to 50 %), whereas in the group of females, on the contrary, both the mass and the weight coefficient of this organ varied slightly (Table 3).

Thus, for each of the three groups of studied indicators (Tables 1–3) Sexual differences were noted in Balb/c mice. At the same time, both males and females had a number of characteristics with strong variability, which could indicate the heterogeneity of the state of animals within the compared groups.

DISCUSSION

Earlier, during long-term studies conducted on white laboratory rats, mongrel and linear (Wistar), as well as in sick and healthy people, criteria of adaptive status were identified, reflecting the nature and intensity of general nonspecific adaptational reactions of the body (AR), which had different values in humans and animals [9; 13; 14]. At the same time, several hematological indicators (primarily, the percentage of

Table 1. Indicators of ROC in intact sexually mature mice of the Balb/c line of different fields ($X_{av.} \pm m$, $Me [X_{min} – X_{max}]$, CV %)

Indicator	Male, *n* = 10	Female, *n* = 10
Erythrocytes (10^9/L)	5,57 ± 0.42 5.8 [3.9–6.4] 22.6 %	6.9 ± 0.42 7.3 [3.8–8.2]* 18.4 %
Hemoglobin (g/L)	119.7 ± 6.8 120 [89–138] 13.9 %	132.3 ± 5.1 137 [97–47] 11.5 %
Mean Corpuscular Hemoglobin (pg)	21.8 ± 0.8 21.4 [19.9–25.2] 11.0 %	19.5 ± 0.7 18.8 [17.5–25.5]* 11.2 %
Platelets (10^9/L)	808.0 ± 79.7 736 [601–1301] 29.6 %	854.3 ± 103.9 832.5 [443–1363] 36.5 %
Leukocytes (10^9/L)	4.8 ± 0.44 5.3 [3–6] 27.0 %	3.8 ± 0.54 3.35 [1.8–7] 42.6 %
Lymphocytes %	69.6 ± 4.0 71.4 [49.4–84.7] 17.2 %	83.6 ± 1.33 84.2 [77.4–87.7]* 5.0 %
Monocytes %	13.3 ± 1.7 1.9 [6.5–20.5] 38.3 %	7.24 ± 0.50 7.0 [5.4–10.2]* 20.6 %

Note: * – differs from the indicators in male mice, $p \leq 0.01$.

lymphocytes) were shown to be related to processes in the neuroendocrine and immune systems that determine the development of a particular AR, the body's resistance to the action of various damaging factors and are reflected in such simple characteristics as the weight coefficients of the thymus and adrenal glands and the ratio of the masses of these organs. Differences in the character and tensions of AR in animals close in age and conditions of existence are determined by differences in the individual sensitivity of the organism to the action of exogenous and endogenous factors [9; 14]. In pathological conditions, such differences can cause differences in the level of nonspecific antitumor resistance of the body, and, consequently, in the clinical course of the disease and the effectiveness of treatment, which requires an individual approach to determining the parameters (regimens, doses, intensity, etc.) of the therapeutic effect.

Unlike laboratory rats, in mice, mongrel and linear, studies have not been conducted to determine specific values of parameters reflecting the nature and intensity of AR. Nevertheless, given the universal nature of systemic adaptation processes, it is advisable to try to use the previously identified informative indicators of adaptation status for a preliminary, indicative assessment of the differences noted in intact Balb/c mice.

When determining the mass and weight coefficients of the studied organs, attention was drawn to the more significant value of most of these indicators in females compared to males. At the same time, the difference in the mass of the thymus was leveled when switching to the weight coefficient of this organ,

Table 2. Some indicators of biochemical blood analysis in intact sexually mature Balb/c mice of different fields ($X_{av.} \pm m$, Me [$X_{min} – X_{max}$], CV %)

Indicator	Male, *n* = 10	Female, *n* = 10
Complete protein (g/dL)	4.33 ± 0.23 4.2 [3.4 –5.4] 15.9 %	5.01 ± 0.18^{T} 5 [3.8 –5.5] 10.2 %
Albumin (g/dL)	2.30 ± 0.22 2.5 [1.1 –3.2] 28.7 %	3.37 ± 0.18 3.4 [2.4 –4.0]* 15 %
Globulins (g/dL)	2.00 ± 0.23 1.7 [1.3 –3] 34.5 %	1.62 ± 0.10 1.5 [1.4 –2.2] 17.6 %
Albumin/globulin index	1.30 ± 0.19 1.37 [0.37 –2.00] 43.8 %	2.14 ± 0.18 2.20 [1.36 –2.86]* 24.1 %
Alkaline Phosphatase (u/L)	79.70 ± 6.00 83 [50 –98] 22.6 %	53.44 ± 2.63 55 [47 –61] 13.9 %
Alanine Aminotransferase (u/L)	38.8 ± 2.1 39 [29 –48] 16.2 %	31.8 ± 2.3 32 [21 –44] 20.6 %
Amilase (u/L)	929 ± 101 887 [543 –1457] 32.6 %	1124 ± 72 1098 [875 –1502] 18 %
Urea (mg/dL)	21.9 ± 1.9 20 [15 –33] 26 %	1.8 ± 1.1 16 [11 –21]* 19.2 %

Note: * – differs from the indicators in male mice, $p < 0.05–0.01$; ^{T} – differs from the values in male mice as a tendency, $p < 0.1$.

in contrast to similar, but more pronounced differences in the weight characteristics of the adrenal glands and spleen. Considering the known information about an active decrease in thymus mass in laboratory rats and mice over a period of 1.5–6 months [17], as well as a slightly more significant age in females compared to males, one would expect a decrease in their thymus weight characteristics compared to those in males, which, however, did not happen. This suggests a high level of lymphoproliferative activity in the thymus of female mice.

When analyzing the weight characteristics of the adrenal glands of the studied animals, it should be noted that female mice of the Balb/c line have the largest adrenal glands among other mice of widely used lines [1]. At the same time, we were unable to find information with a direct indication of the established or possible cause of the increased size of this organ in these animals compared to the size of the adrenal glands in males of the same line. It is possible that such an increase is to some extent due to the increased production of aldosterone, characteristic specifically for females of the Balb/c line [18]. Due to this feature, the weight coefficient of the adrenal glands cannot be fully used as an indicator of the adaptive status of female mice of the line under consideration, which also reduces the informativeness of another indicator – the ratio of thymus mass to adrenal mass. An even greater difficulty is caused by the interpretation of the sex difference in the weight characteristics of the spleen in mice of the Balb/c line, which, as is known [1], is characterized by large sizes exceeding this indicator in mice of most known lines. We have not been able to find any information in the literature devoted to this issue and shedding light on the reason for the larger spleen size in Balb/c females, except for some indications of higher reactivity of the spleen in these animals compared to males of the same lineage [19].

Despite the mentioned difficulties associated with the undeveloped criteria of adaptive status and sexual characteristics of the weight characteristics of the immune system and adrenal glands in mice of

Table 3. Weight and weight coefficients of some internal organs in intact sexually mature mice of the Balb/c line of different fields ($X_{av.} \pm m$, $Me\ [X_{min} – X_{max}]$, $CV\ \%$)

Показатель		Male	Female
Animal weight (g)		27,9 ± 1.5 27.7 [22.5–34] 13.2 %	32.2 ± 0.7 33 [27.5–34]* 6.8 %
Thymus	Mass (mg)	28.4 ± 3.6 30 [13–42] 38.0 %	42.1 ± 5.7 43 [24–68]* 35.7 %
	Weight coefficient ×10^{-4}	10.1 ± 1.1 9.1 [5.8–14.2] 32.7 %	13.3 ± 2.1 13.2 [8.5–24.7] 41.7 %
Adrenal glands	Mass (mg)	14.2 ± 1.15 15 [10–19] 24.3 %	28.9 ± 1.87 28 [21–32]* 18.4 %
	Weight coefficient ×10^{-4}	5.1 ± 0.23 5.1 [4.4–5.9] 13.5 %	9.0 ± 0.6 8.3 [7.6–11.8]* 16.8 %
Thymus mass/Adrenal glands mass		2.0 ± 0.19 2.1 [1.3–2.8] 28.5 %	1.6 ± 0.3 1.6 [0.6–3.2] 51.4 %
Spleen	Mass (mg)	84.2 ± 14 94 [39.4–130] 50.0 %	156 ± 5.0 154 [131–179]* 9.5 %
	Weight coefficient ×10^{-4}	29.4 ± 4.0 36.9 [14.3–39.3] 40.8 %	48.8 ± 1.9 49.7 [39.7–54.2]* 10.3 %

Note: * – differs from the indicators in male mice, $p < 0.05–0.001$.

the Balb/c line, the results obtained, in our opinion, still allow us to make a number of assumptions about the differences in the condition of intact animals of different sexes belonging to the line under consideration. As already noted, the group of females was somewhat more homogeneous in terms of the values of the studied indicators compared to the group of males and differed in relative stability of animal weight and lower variability of a few indicators compared to the characteristics of males (Tables 1–3). In our opinion, on the day of the examination, the adaptive status of females was slightly higher than the adaptive status of males, because despite a slightly more significant age compared to males, as well as such a constitutional feature of Balb/c females as an increased weight of the adrenal glands, the ratio of thymus mass to adrenal mass in these animals did not statistically significantly differ from the ratio of the mass of these organs in males. In addition, females demonstrated a higher and more stable percentage of lymphocytes in the blood than males, corresponding to the range of maximum values of this indicator for Balb/c mice [1; 20]. This allowed us to assume about the development of AR increased activation in the studied group of females [9; 16].

Signs such as a statistically significant decrease in the percentage of lymphocytes in the blood, monocytosis, an increase in the content of urea with a tendency to decrease the level of total protein compared to the indicators in females indicated a slightly lower adaptive status of males compared to that noted in females. At the same time, the shift of the albumin-globulin index towards globulins, an increase in the level of urea and alkaline phosphatase, as well as signs of moderate monocytosis could be associated with some tension of antistress AR in males [2; 9; 16] and reflect the activation of metabolic and immune processes, which has a compensatory value. The reasons for such a decrease in the adaptive status of males compared to females could be related to their lower stress resistance and greater dependence on social status in the group than in females [1; 2; 21].

A comprehensive examination of the results gives the impression of the existence of sexual differences in the regulatory mechanisms that dominate in females and males in physiological conditions. It can be assumed that in males there is a certain shift in immunoreactivity towards the B-cell and myeloid links of immunity in comparison with the regulatory circuit in females, who probably have more active T-cell immune processes. This may be evidenced by an increase in the content of immunoglobulins relative to albumins and an increase in the level of alkaline phosphatase, which affects the activity of B-lymphocytes and neutrophils [22], in the blood of males compared with females, while the indicators of the condition of females indicated high lymphoproliferative activity in the thymus, accompanied by a maximum percentage of lymphocytes in the blood. This assumption is consistent with the literature data on the gender-related features of immunity in humans and animals and the greater severity of T-cell processes in female individuals, and B-cell immune processes in male individuals [6; 21; 22]. The high variability of a number of the studied indicators (observed in males of the Balb/c line more often than in females) may indicate the existence of different variants of integration of reactivity mechanisms in animals of the same sex, which may affect the effectiveness of systemic regulation under the action of damaging factors. To clarify this issue, it is necessary to develop criteria for the nature and intensity of AR, similarly used in humans and white laboratory rats [9; 14].

CONCLUSIONS

The study of weak and moderate shifts in traditional laboratory indicators reflecting the adaptive status and characteristics of the blood of mature males and females of the Balb/c line under physiological norm conditions allowed us to identify individual and sexual characteristics of systemic regulatory processes that may be important for the body's resistance to damaging factors, including the malignant process. To objectify the connection of sexual and individual differences of the studied indicators with the systemic mechanisms of nonspecific, including antitumor, resistance, it is advisable to develop criteria for the character and tensions of AR, similar to those used in humans and white laboratory rats. The results obtained indicate the relevance of the issue of sex differences in the reactivity of T-cell, B-cell and myeloid links of immunity and the influence of the severity of immune processes dominating in physiological conditions on carcinogenesis, which may contribute to the development of new effective methods of antitumor treatment.

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Trepitaki L. K. – performed work with experimental animals, necropsy, participation in statistical processing of results;

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