

COMPARATIVE STUDY OF BIOCHEMICAL AND MORPHOLOGICAL PARAMETERS IN RATS WITH WALKER 256 AND WALKER 256/DOX CARCINOSARCOMA

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Aim: To evaluate the changes of some biochemical blood plasma parameters and morphological structure of the internal organs of rats with transplanted doxorubicin (DOX)-sensitive (Walker 256) and doxorubicin-resistant (Walker 256/DOX) strains of Walker 256 carcinosarcoma. **Materials and Methods:** The study was performed on female Wistar rats with transplanted Walker 256 or Walker 256/DOX and intact animals (control). On the 9th day after transplantation of tumor cells, a comparative analysis of some blood plasma biochemical parameters and morphological examination of the liver, kidneys, myocardium and spleen of rats was carried out. **Results:** Walker 256 growth, in comparison with Walker 256/DOX, is accompanied by more pronounced systemic effect on tumor-bearing rats. Uric acid concentration in the blood plasma of Walker 256 bearing rats was significantly (by 15.5%) higher than in Walker 256/DOX bearing rats. Aspartate aminotransferase activity in the Walker 256 group was significantly (by 107.2%) higher than in Walker 256/DOX group, but alanine aminotransferase activity was 58.5% lower. 56.7% decrease of alkaline phosphatase in rats with Walker 256, and 21% increase of this index in rats with Walker 256/DOX were observed. The growth of Walker 256 carcinosarcoma led to greater structural damage of the liver, kidneys and spleen in experimental animals compared with Walker 256/DOX strain. **Conclusion:** Tumor growth in rats with Walker 256/DOX leads to less pronounced changes in the biochemical parameters of rat blood plasma and morphological structure of internal organs compared with wild-type carcinosarcoma.

Key Words: Walker 256 and 256/DOX carcinosarcoma, doxorubicin, drug resistance.

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Malignant tumor growth, in addition to its local action on the damaged organ, in which or next to which the tumor develops, is accompanied by polytropic systemic effects of the tumor on the host as a whole and its individual organs and systems. The corresponding reaction of the tumor-bearing host is manifested in the form of significant metabolic disorders leading to the development of “metabolic intoxication” [1], and profound structural and functional changes in organs located distantly from the primary tumor [2].

Among the experimental works devoted to the study of the tumor-host interaction, a significant number was performed on a model of transplanted Walker 256 carcinosarcoma (Walker 256), which is still widely used in experimental oncology. Its important feature is the similarity of the biological features of the tumor in rats and humans, and the possibility to transplant Walker 256 cells to different strains of rats [3]. Since Walker 256 is a mixed tumor with sarcomatous and parenchymal components exerting different sensitivity to chemotherapeutic drugs, it is widely used for preclinical evaluation of new antitumor agents [4].

The results of the studies of the systemic effects of Walker 256 carcinosarcoma demonstrated its ability to promote the development of anorexia and cachexia [5], which may be associated with the release of anti-inflammatory cytokines and prostaglandins [6]. On the 3rd day after grafting Walker 256 cells, rats begin to develop anemia, which progresses rapidly, correlating with an increase in anorexia [7]. Walker 256 causes the development of oxidative stress, particularly in the brain of animals, due to the stimulation of lipid oxidation with a simultaneous imbalance in the enzymatic system of antioxidant defense [8, 9]. Along with metabolic changes, the growth of carcinosarcoma causes structural and functional disorders of internal organs. A number of publications have reported the disorders of the kidneys [10], liver [11] and myocardium [12, 13].

Drug resistance of tumors is an issue that has long been in the spotlight of scientists and clinicians. One of the cytostatics widely used in a complex treatment of cancer of mammary gland, prostate, lung, ovaries and leukemia, is an anthracycline antibiotic doxorubicin (DOX). However, there are at least two factors that can significantly limit its use. The first is associated with high cardiovascular toxicity of DOX that may interfere with a full course of antitumor chemotherapy [14, 15], the second — with the development of drug resistance involving the mechanisms that promote the induction of proliferation, cell cycle progression and prevention of apoptosis [16].

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Abbreviations used: ALT — alanine aminotransferase; AST — aspartate aminotransferase; DOX — doxorubicin; Walker 256 — the original (wild-type) strain of Walker 256 carcinosarcoma; Walker 256/DOX — doxorubicin-resistant strain.

Recent studies of DOX resistance of Walker 256 have shown a decreased content of K^+ , Mg^{++} and glucose in the serum of tumor-bearing rats [17], increased content of ferritin and transferrin at the beginning of resistance formation and its significant increase at the end of resistance formation [18]. Changes in the molecular architecture of serum albumin of rats with transplanted Walker 256 were noted to be more pronounced in DOX-resistant variant [19]. The above suggests that the resistance formation is the result of the tumor — host interaction that occurs against the background of the action of antitumor drugs. Therefore, monitoring and analysis of the data on structural and metabolic changes due to the development of DOX resistance may help to find the ways to overcome such resistance.

MATERIALS AND METHODS

The study was performed on female Wistar rats weighing 190 ± 15 g, obtained from the vivarium of the RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology NAS of Ukraine. The animals were kept in accordance with the “Standard rules for the organization, equipment and maintenance of experimental biological clinics (vivariums)”. When working with animals, all the requirements of the “European Convention for the Protection of Vertebrate Animals Used in Experimental and Other Scientific Purposes” (Strasbourg, 1986), the basic rules of good laboratory practice GLP (1981), the law of Ukraine № 3447-IV of 21.02.2006 “On the protection of animals from cruel treatment” were held.

In the study, Walker 256 carcinosarcoma cell line obtained from the Bank of Cell Lines from Human and Animal Tissues of IEPOR was used. Suspension of Walker 256 cells was injected subcutaneously into the thighs of rats (1.0×10^6 cells in 0.2 ml of saline per animal). The experimental model of doxorubicin-resistant strain (Walker 256/DOX) was created as described previously [17].

Animals were distributed into three groups: group 1 (control) — intact rats ($n = 5$); group 2 (experimental 1) — rats with Walker 256 ($n = 5$); and group 3 (experimental 2) — rats with Walker 256/DOX ($n = 5$).

On the 9th day after Walker 256 and Walker 256/DOX inoculation, the blood was taken under ether narcosis from vena cava inferior.

Plasma concentrations of glucose, uric acid, cholesterol, amylase, lactate, total protein, albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, triglycerides, and urea were measured using Beckman Coulter AU-480 analyzer and Beckman Coulter Kits.

Internal organs (liver, kidney, myocardium and spleen) were isolated, washed with cold saline and fixed in 4% buffered formalin.

Tumors of rats from experimental groups were excised and weighed. For histological examination, the tissues were fixed in formalin, dehydrated in 70% ethanol and embedded into paraffin according to routine technique. Serial 5 μ m sections were stained with hematoxylin and eosin and examined by light microscopy. The histological samples were analyzed and photographed under a light microscope using a System Microscope with an Olympus BX41 system, equipped with a Camedia C-5050 zoom digital camera and Olympus DP 80 FT 3.2 software based on a Pentium 4 computer running Windows XP.

Statistical data analysis has been performed using STATISTICA 7.5. For calculation and comparison of the reliability of the average values of the differences Student's *t*-test was used; the differences with probability not less than 95% ($p < 0.05$) were considered significant.

RESULTS

The study included an analysis of a number of biochemical parameters of blood plasma and morphological structure of the liver, kidneys, myocardium and spleen of Wistar rats on day 9 after transplantation of Walker 256 and Walker 256/DOX. The biochemical indexes of blood plasma of rats of both experimental and intact control groups are presented in Table 1.

Amylase activity and levels of glucose, cholesterol and lactate in the blood plasma of the tumor-bearing rats increased slightly but not significantly in comparison with the intact animals. In both experimental groups, the triglyceride level in the blood plasma was significantly higher than in the control group (by 36% in average). Simultaneous small increase of cholesterol level and decrease of total protein content by 25.7% and 19.7%, especially albumin by 23.5% and 34.63%, in the Walker 256 and Walker 256/DOX groups correspondingly, may indicate the progressive development

Table 1. Plasma/serum biochemical parameters of intact rats and rats with Walker 256/DOX and Walker 256 on the 9th day after tumor cell inoculation

Index	Group		
	Intact	Walker 256	Walker 256/DOX
Glucose, mmol/l	7.85 ± 0.35	8.35 ± 0.05	8.27 ± 0.29
Uric acid, mmol/l	154.5 ± 15.10	$202.2 \pm 4.5^{*^{\wedge}}$	$175 \pm 3.39^*$
Cholesterol, mmol/l	1.9 ± 0.10	2.2 ± 0.20	2.33 ± 0.33
Amylase, U/l	972.0 ± 10.20	1038.5 ± 10.50	976 ± 10.80
Lactate, U/l	13.25 ± 4.25	14.25 ± 2.25	14.37 ± 1.10
Total protein, g/l	68.57 ± 3.27	$51.0 \pm 3.10^*$	$55.13 \pm 2.3^*$
Albumin, g/l	36.5 ± 0.5	$28.05 \pm 1.1^*$	$23.86 \pm 1.3^*$
ALT, U/l	57.25 ± 1.11	$14.5 \pm 2.25^{*^{\wedge}}$	$48.00 \pm 1.7^*$
AST, U/l	139.75 ± 53.00	$193.50 \pm 31.00^{*^{\wedge}}$	$343.33 \pm 22.5^*$
Alkaline phosphatase, U/l	184.00 ± 18.30	$79.5 \pm 6.50^{*^{\wedge}}$	$222.70 \pm 31.2^*$
Triglycerides, mmol/l	1.32 ± 0.16	$1.8 \pm 0.60^*$	$1.8 \pm 0.60^*$
Urea, mmol/l	5.55 ± 0.75	5.3 ± 0.10	5.3 ± 0.10

Note: *The difference is significant compared with the control group, $p < 0.05$.

[^]The difference between Walker 256 and Walker 256/DOX groups is significant, $p < 0.05$.

of nephrotic syndrome [20], which often accompanies malignant tumor growth at its different stages.

The significant increase of the uric acid concentration by 30.9% and 13.3% was observed in the animal blood plasma, in the Walker 256 and Walker 256/DOX groups correspondingly. This index was significantly higher (by 15.5%) in the Walker 256 group than in the Walker 256/DOX group. This may be due to more pronounced renal failure in this group [21, 22] and/or probable myocardial damage [23–26]. Blood plasma AST activity in the Walker 256 group was 38.5% higher and in the Walker 256/DOX group 145.7% higher than in the control. At the same time, ALT activity was, in contrary, lower by 74.6% and by 16.1% correspondingly. Sharp drop in the ALT activity in the Walker 256 bearing rats, which was 58.5% less than in the Walker 256/DOX group, is, most probably, related to pathological processes in the kidneys and liver, and significant AST increase (by 107.2%) — with myocardial damage.

A decrease of alkaline phosphatase activity by 56.7% has been detected in the plasma of rats with Walker 256, while in Walker 256/DOX group this index was by 21% higher than in intact animals and by 180% higher than in Walker 256 group. It is believed that the decrease in alkaline phosphatase levels that occurred

in the group of rats with Walker 256/DOX may be due to the development of anemia [27, 28].

It should be noted that the tumor mass on the 9th day after transplantation was not significantly different between the experimental groups and was equal to 4.0 ± 0.3 g.

The development of Walker 256 and Walker 256/DOX was accompanied by the changes of histological structure of the liver, kidney, myocardium and spleen.

The dilatation of the bile ducts and sinusoidal hemocapillaries in the liver of tumor-bearing animals indicates the disturbance in microcirculatory tract (Fig. 1, *b* and *c*). Notably, the changes in the liver structure of animals with Walker 256 were more pronounced and manifested in a decrease in hepatocyte size, cytoplasmic heterogeneity, nuclear polymorphism and anisonucleosis.

In kidneys of the rats with Walker 256 and Walker 256/DOX, an atrophy of the renal glomeruli (Fig. 2, *b* and *c*) took place. Some tubules had signs of edema, epithelial dystrophy with karyolysis, exfoliation of the apical poles of the nephroepithelium. The structural changes in kidneys of animals with Walker 256 were more expressed.

The myocardium structure of rats in both experimental groups was similar and was characterized

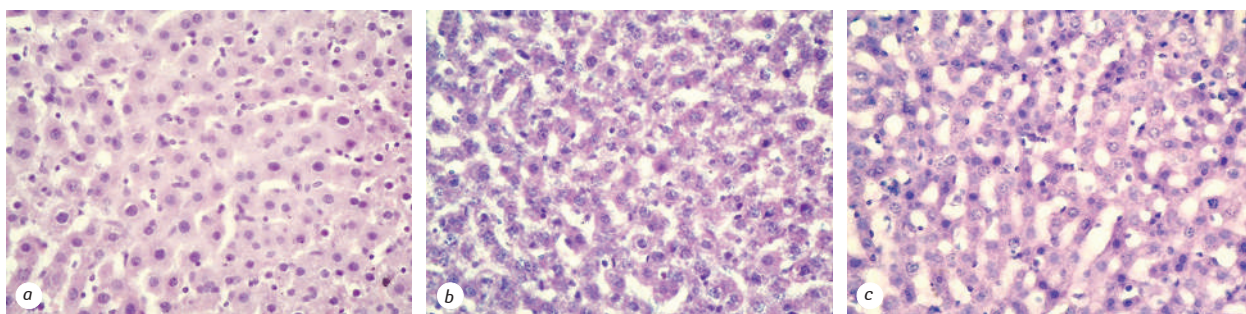


Fig. 1. Morphological structure of rat liver: *a* — control, *b* — Walker 256, *c* — Walker 256/DOX. H&E, $\times 400$

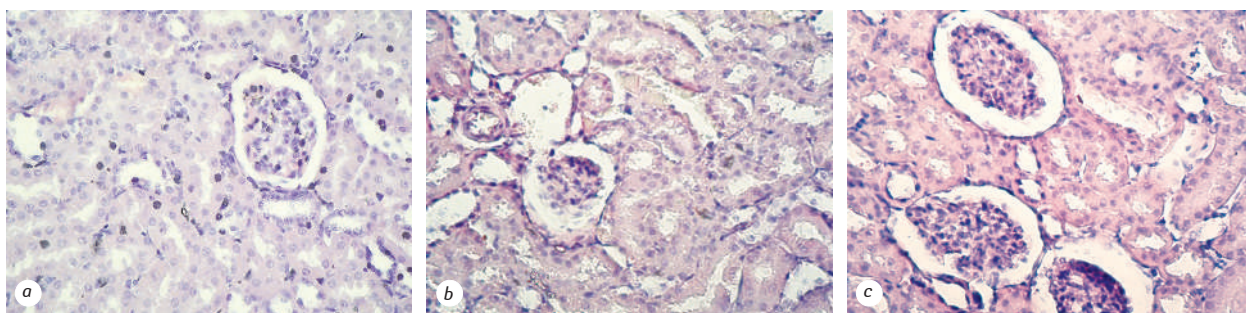


Fig. 2. Morphological structure of rat kidney: *a* — control, *b* — Walker 256, *c* — Walker 256/DOX. H&E, $\times 400$

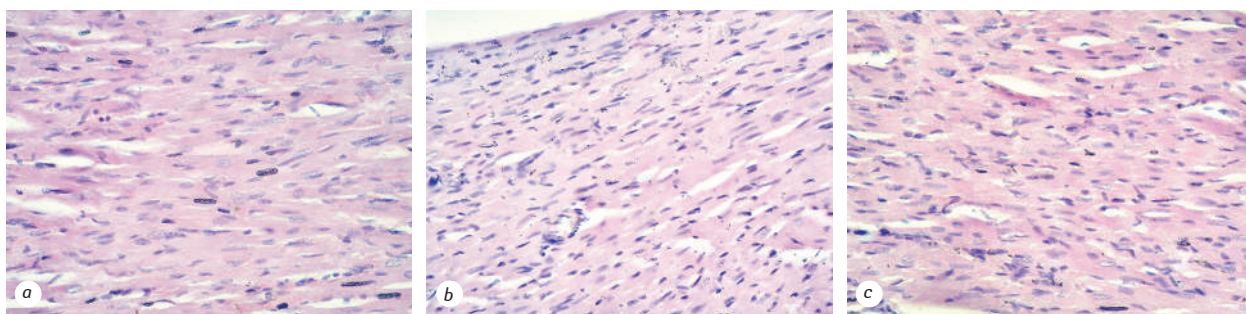


Fig. 3. Morphological structure of rat myocardium: *a* — control, *b* — Walker 256, *c* — Walker 256/DOX. H&E, $\times 400$

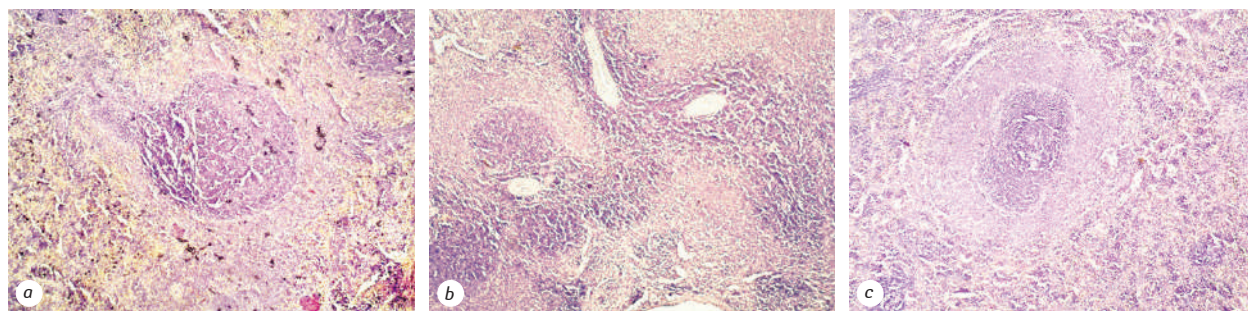


Fig. 4. Morphological structure of rat spleen: *a* — control, *b* — Walker 256, *c* — Walker 256/DOX. H&E, $\times 200$

by areas of inhomogeneous staining of cardiomyocytes and thinning of muscle fiber bundles due to mild-to-moderate atrophy (Fig. 3, *b* and *c*).

The noted decrease in the size of cardiomyocytes, as well as polymorphism of their nuclei with a strongly stained nuclear chromatin is considered a sign of myocardial dysfunction.

In the spleen of tumor-bearing animals from both experimental groups dilated venous sinuses were observed (Fig. 4, *b* and *c*). The white pulp of the Walker 256 rat spleen contained irregularly shaped follicles that fused together and had dilated central arteries. Probably, this is due to the microcirculatory disorders and demonstrates more expressive reaction of the lymphoid tissue to the tumor growth.

DISCUSSION

Malignant tumor development, in addition to its local action leading to the structural and consequent functional damage in the involved organs and tissues, is accompanied by the systemic effects resulting in the profound morphological and functional modifications in the distant organs and tissues.

The results obtained in the framework of our study demonstrated that the development of Walker 256 tumors of both wild-type and DOX-resistant strains, already on day 9 after transplantation, led to the essential biochemical modulations in the blood plasma, structural damages in myocardium and detoxification-involved organs, and spleen reactive response. However, comparative analysis of kidney and liver morphology as well as uric acid level and ALT activity demonstrates that in the rats with the DOX-resistant tumors the excretory organs experience less toxic load on the 9th day after tumor transplantation. There was a less pronounced reactive response of lymphoid tissue to the growth of Walker 256/DOX as well.

Since AST activity was much higher in the rats with Walker 256, one can assume myocardial damage. Nevertheless, no significant difference in morphological structure of myocardium was found between rats with Walker 256 and Walker 256/DOX.

We believe that high alkaline phosphatase level and more expressed spleen reactive response may be related to anemia in the rats with the wild-type carcinosarcoma strain.

The data obtained are in full agreement with our previous results, which indicated more pronounced structural changes in plasma albumin of rats with

Walker 256/DOX [19]. Despite the higher concentration of total protein in the blood plasma of Walker 256/DOX bearing rats in comparison with Walker 256, which is undoubtedly a positive fact, the albumin concentration in the former was significantly lower than in the latter. Earlier it was clearly shown that albumin could transport DOX via hydrophilic and hydrophobic contacts and forming a stable complex. Such drug interaction alters its secondary structure causing a partial protein destabilization [29]. The low levels of the main plasma protein in rats with DOX-resistant carcinosarcoma result in additional ligand loading of each albumin molecule, leading to a drastic change in its conformation, loss of basic acceptor and transport function and protective antioxidant potential. The loss of the association of DOX with the “overloaded” albumin molecule may adversely affect the efficiency of targeted delivery of antibiotic to tumor cells contributing to the development of tumor insensitivity/resistance to DOX.

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ПОРІВНЯЛЬНЕ ДОСЛІДЖЕННЯ БІОХІМІЧНИХ І МОРФОЛОГІЧНИХ ПОКАЗНИКІВ У ЩУРІВ З КАРЦИНОСАРКОМОЮ УОКЕРА 256 ТА ЇЇ ВАРІАНТОМ, РЕЗИСТЕНТНИМ ДО ДОКСОРУБІЦИНУ

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Мета: Оцінити зміни деяких біохімічних показників плазми крові та морфології внутрішніх органів щурів з трансплантованою карциносаркомою Уокера (доксорубіцин (DOX)-чутливим (Walker 256) та резистентним до доксорубіцину (Walker 256/DOX) штамами). **Матеріали та методи:** Дослідження проводили на самках щурів Wistar з трансплантованими пухлинами Walker 256 або Walker 256/DOX. На 9-й день після трансплантації клітин пухлини аналізували деякі біохімічні показники плазми крові та проводили морфологічне дослідження печінки, нирок, міокарда та селезінки щурів. **Результати:** Ріст карциносаркоми Walker 256 порівняно з Walker 256/DOX супроводжується більш вираженим системним впливом на щурів з пухлиною. Концентрація сечової кислоти у плазмі крові щурів з пухлиною Walker 256 була значно (на 15,5%) вищою, ніж у щурів з Walker 256/DOX. Активність аспартатамінотрансферази у групі Walker 256 була значно (на 107,2%) вищою, ніж у групі Walker 256/DOX, але активність аланінамінотрансферази була на 58,5% нижчою. Спостерігали зниження на 56,7% активності лужної фосфатази у щурів з Walker 256 та збільшення на 21% цього показника у щурів з Walker 256/DOX. Ріст карциносаркоми Walker 256 призводив до більш виражених структурних пошкоджень печінки, нирок та селезінки у експериментальних тварин у порівнянні зі штамом Walker 256/DOX. **Висновок:** Ріст пухлин Walker 256/DOX призводить до менш виражених змін біохімічних показників плазми крові щурів та морфологічної структури внутрішніх органів у порівнянні з карциносаркомою Walker 256.

Ключові слова: карциносаркома Walker 256 і 256/DOX, доксорубіцин, резистентність до лікарських препаратів.