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ORIGINAL ARTICLE

MODELING OF MULTIPLE PRIMARY MALIGNANT TUMORS IN EXPERIMENT

E. M. Frantsiyants, I. V. Kaplieva, V. A. Bondovkina, E. I. Surikova, I. V. Neskubina, L. K. Trepitaki, Yu. A. Pogorelova, N. D. Cheryarina, E. A. Sheiko✉, I. M. Kotieva, K. A. Shumarin

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ esheiko@inbox.ru

ABSTRACT

Purpose of the study. Creation and study of models of primary multiple malignant tumors (MMPT model) under experimental conditions.

Materials and methods. The study was carried out involving male and female BALB/c Nude mice (n = 42). Experimental groups of mice: with melanoma B16/F10 (B16/F10), males (control 1) and females (control 3) by n = 7; control 2 – with sarcoma 45 (C45), males n = 7; control 4 – with Guerin carcinoma (KG), females n = 7; basic: MMPT model No. 1 – B16/F10 and S45, males n = 7, and MMPT model No. 2 – B16/F10 and GC, females n = 7. 0.5 ml suspension of murine B16/F10 melanoma tumor cells diluted in the saline proportions 1:20 was injected under the skin of the left dorsal side to all animals with MMPT model, as well as 0.5 ml of a suspension containing 0.50×10^6 S45 or GC tumor cells in the saline under the skin on the right dorsum. Control groups received the same amount of tumors as the MMPT model.

Results. Tumors in male mice in MMPT model No. 1 appeared simultaneously and significantly earlier than in controls: B16/F10 melanoma by 3 times, S45 by 2 times. Tumor zises in MMPT model No. 1 were larger than in the corresponding controls: by 8.5 times at the area of B16/F10 melanoma inoculation and by 2.2 times at the area of S45 inoculation. Melanoma metastasized under the S45 capsule. Tumor at the area of GC transplantation in MMPT model No. 2 grew 5 times faster than at the area of B16/F10 melanoma injection; both tumors appeared on average 3 times earlier than in control groups 3 and 4. Tumor volumes in MMPT model No. 2 were larger than in the corresponding controls: by 7.5 times at the area of B16/F10 melanoma inoculation and by 2.2 times at the area of GC inoculation. However, almost the entire volume of the tumor node in the area of B16/F10 melanoma transplantation was represented by GC tumor tissue due to metastasis from the primary GC tumor. Melanoma remained as a small black spot with a diameter of 5–6 mm at the area of its inoculation under the skin. The average survival of mice in MMPT models No. 1 and No. 2 was 1.5–2 times ($p < 0.05$) lower than in the corresponding controls.

Conclusions. Sequential subcutaneous transplantation of mouse B16/F10 melanoma and rat sarcoma 45 to BALB/c Nude mice increased the malignant potential of each tumor: the time of their onset was shorter, and the growth rate of tumors increased which decreased the survival of animals. Sequential subcutaneous transplantation of mouse B16/F10 melanoma and Guerin's rat carcinoma to female BALB/c Nude mice suppressed tumor growth of B16/F10 melanoma and increased the malignant potential of rat GC.

Keywords:
BALB/c Nude mice, sarcoma 45, Guerin's carcinoma, B16/F10 melanoma, multiple primary tumors, males, females

For correspondence:
Elena A. Sheiko – Cand. Sci. (Biol.), junior research fellow of the laboratory of Malignant Tumor Pathogenesis Study National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: esheiko@inbox.ru
ORCID: https://orcid.org/0000-0002-9616-8996
SPIN: 7293-3480, AuthorID: 479978

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ОРИГИНАЛЬНАЯ СТАТЬЯ

МОДЕЛИРОВАНИЕ ПЕРВИЧНО-МНОЖЕСТВЕННЫХ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ В ЭКСПЕРИМЕНТЕ

Е. М. Франциянц, И. В. Каплиева, В. А. Бандовкина, Е. И. Сурикова, И. В. Нескубина, Л. К. Трепитаки, Ю. А. Погорелова, Н. Д. Черярина, Е. А. Шейко✉, И. М. Котиева, К. А. Шумарин

НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
✉ esheiko@inbox.ru

РЕЗЮМЕ

Цель исследования. Создание и изучение моделей первично-множественных злокачественных опухолей (модель ПМЗО) в условиях эксперимента.

Материалы и методы. Работа выполнена на мышах обоего пола линии BALB/c Nude (*n* = 42). Экспериментальные группы мышей: с меланомой B16/F10 (B16/F10), самцы (контроль 1) и самки (контроль 3) по *n* = 7; контроль 2 – с саркомой 45 (С45), самцы *n* = 7; контроль 4 – с карциномой Герена (КГ), самки *n* = 7; основные: модель ПМЗО № 1 – B16/F10 и С45, самцы *n* = 7 и модель ПМЗО № 2 – B16/F10 и КГ, самки *n* = 7. Каждому животному с моделью ПМЗО под кожу спины слева перевивали по 0,5 мл взвеси клеток B16/F10 в физ. растворе в разведении 1:20, справа – по 0,5 мл взвеси, содержащей 0,5 × 10^6 клеток С45 или КГ в физ. растворе. Контрольным мышам перевивали опухоли в том же количестве и объёме, что и в модели ПМЗО.

Результаты. В модели ПМЗО № 1 опухоли появлялись одновременно, быстрее, чем в контроле: B16/F10 – в 3 раза, С45 – в 2 раза. Объём каждой опухоли в модели ПМЗО № 1 превышал объём опухолей в соответствующих контролях: B16/F10 – в 8,5 раза, С45 – в 2,2 раза. B16/F10 метастазировала под капсулу опухоли С45. В модели ПМЗО № 2 опухоль в месте перевивки КГ вырастала в 5 раз быстрее, чем в месте перевивки B16/F10, при этом, обе опухоли появлялись в среднем в 3 раза раньше, чем в контролях 3 и 4. Объём опухолей в модели ПМЗО № 2 превышал объём опухолей в соответствующих контролях: B16/F10 – в 7,5 раза, КГ – в 2,1 раза. Однако, большую часть опухоли в зоне введения B16/F10 занимала ткань КГ вследствие её метастатического отсева из первичной опухоли. Ткань B16/F10 сохранялась в виде небольшого чёрного пятна в месте её введения под кожей. Средняя продолжительность жизни мышей в моделях ПМЗО № 1 и № 2 была в 1,5–2 раза ($p < 0,05$) меньше, чем в соответствующих контролях.

Заключение. Последовательная подкожная перевивка мышиной B16/F10 и крысиной С45 самцам мышей BALB/c Nude увеличивала злокачественный потенциал каждой из опухолей: опухоли появлялись раньше и росли активнее, что способствовало уменьшению продолжительности жизни животных. Последовательная подкожная перевивка мышиной B16/F10 и крысиной КГ самкам мышей линии BALB/c Nude способствовала подавлению опухолевого роста мышиной B16/F10 и увеличивала злокачественный потенциал крысиной КГ.

Ключевые слова:
мыши линии BALB/c Nude, саркома 45, карцинома Герена, меланома B16/F10, полинеоплазии, самцы, самки

Для корреспонденции:
Шейко Елена Александровна – к.б.н., младший научный сотрудник лаборатории изучения патогенеза злокачественных опухолей ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14 линия, д. 63
E-mail: esheiko@inbox.ru
ORCID: https://orcid.org/0000-0002-9616-8996
SPIN: 7293-3480, AuthorID: 479978

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RELEVANCE

Despite the fact that malignant tumors, as a disease, have been known for a long time, their experimental reproduction has not been possible for a long time. That is why the creation of this pathological process in an experiment became a major scientific achievement at the beginning of the last century. Experimental models of tumors make it possible to find out the causes, study the pathogenesis of the tumor process, and develop methods for its prevention and treatment [1]. Animal models are a powerful tool for studying the biology of neoplasms and the mechanisms of influence of various pathogenic factors on them [2–5], assessing the toxicity and effectiveness of new antitumor agents in preclinical studies [4–8]. For these purposes, mouse and rat models are most often used [9; 10]. Primary multiple malignant tumors (MMPT) were first described by Billroth T. and Reimer G. in 1889 and studied in details by Warren S., Gates O. in 1932. Based on the criteria proposed by these authors, the diagnosis of MMPT can be made if each tumor during histological examination has clear evidence of malignancy, is located separately from another tumor and is not a metastatic dropout. Experimental models of multiple homogeneous tumors-multiple myeloma (MMBD) in NSG mice have been developed, which allow us to investigate the mechanism of oncogenesis of this pathology [11; 12]. In this study, it was found that, compared with single, multiple homogeneous tumors progress more slowly, but subsequently a more severe form of MMBD develops. Since the number of cases of MMPT increases every year, the issue of developing experimental models to assess the pathogenesis of this oncological disease in several tumors of different genesis in one animal remains relevant. Experimental oncology has a sufficiently large number of models that can be used to solve many problems, but one of the unresolved ones is the problem of the development of malignant growth in various immunodeficiency conditions. Primary immunodeficiency states are a group of heterogeneous diseases characterized by recurrent infections, autoimmunity, the course of which is determined by lymphoproliferative diseases and other malignant neoplasms. Immunodeficiency has prognostic and practical consequences [13; 14]. Thus, the increasing incidence of MMPT on the background of primary immunodeficiency dictates the need to study the pathogenesis of this oncological pathology.

The purpose of the study: to create and study models of primary multiple malignant tumors in experimental conditions.

MATERIALS AND METHODS

The work was performed on BALB/c Nude mice with genetically determined thymus aplasia (*n* = 42), of which males (*n* = 21) and females (*n* = 21). Experimental groups of mice: with melanoma B16/F10 (B16/F10) – males, control 1, and females, control 3, *n* = 7; with sarcoma 45 (S45) – males, control 2, *n* = 7; with Guerin carcinoma (GC) – females, control 4, *n* = 7 and the MMPT models: MMPT model No. 1 (B16/F10 and S45), *n* = 7 and MMPT model No. 2 (B16/F10 and GC), *n* = 7. 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).

Reproduction of MT No. 1 consisted in successive subcutaneous inoculation of B16/F10 and S45 to male mice: 0.5 ml of suspension of B16/F10 at a dilution of 1:20 in phys. the solution was injected below the angle of the left scapula, 0.5 ml of suspension S45 containing 0.5×10^6 cells was injected below the angle of the right scapula. The control was male mice with either B16/F10 or S45 in the same dose and volume as in MMPT model No. 1. To reproduce MMPT model No. 2, female mice were used, which were sequentially transplanted with B16/F10 and GC. The method of re-grafting was carried out, as in MMPT model No. 1. However, if below the angle of the left shoulder blade, 0.5 ml of suspension B16/F10 was still injected into the physical. In a dilution solution of 1:20, then 0.5 ml of a GC suspension containing 0.5×10^6 cells was injected below the angle of the right scapula. The control was female mice with either B16/F10 or GC in the same dose and volume as mice with MMPT model No. 2.

Statistical processing of the obtained results was carried out using the Student's parametric criterion on a personal computer using the STATISTICA 10.0 program and the nonparametric Wilcoxon-Mann-Whitney criterion. All the results obtained were checked for compliance with the law on normal distribution. Some of the indicators corresponded to the law, some did not. For those indicators that corresponded to the normal distribution, we used parametric statistics, for those indicators whose distribution did not cor-

respond to the normal distribution, we used nonparametric statistics. The differences between the two samples were considered statistically significant at $p < 0.05$.

RESEARCH RESULTS AND DISCUSSION

When reproducing MMPT model No. 1, the following results were obtained, which are presented in Table 1.

As follows from Table 1, tumors B16/F10 and S45, transplanted in an independent version, appeared approximately at the same time. At the same time, after B16/F10 transplantation, tumors began to be palpated from 11 days (3 mice, 42.8 %), from 45 – from 7 days (1 mouse, 14.3 %) and 10 days (2 mice, 28.6 %). The term of the end of the appearance of tumors in male mice with B16 / F10 is 14 days (1 mouse, 14.3 %) and 15 days (1 mouse, 14.3 %), in male mice with S45–13 days (1 mouse, 14.3 %). In all mice with MMPT model No. 1, tumors appeared earlier, already 1 week after transplantation. At the same time, the tumor B16/F10 began to be determined in the form of a black millet grain starting from 3 days after the transfer (2 mice, 28.6 %), and S45 – in the form of a white string 4–5 mm long from 4 days after the transfer (3 mice, 42.8 %). The deadline for the appearance of both tumors is 7 days after the transfer (1 mouse, 14.3 %). Thus, in MMPT model No. 1, with sequential grafting of tumors, tumors B16/F10 appeared 3 times faster, and S45 2 times faster than with independent grafting (Table 1). There was no statistically significant difference in the timing of the appearance of tumors of various histological structures, either in an independent or combined variant.

The volume of tumors in all animals was measured before the death of the first mice with MMPT model No. 1 – on the 20th day after transplantation. It was found that the volume of each tumor transplanted sequentially into one mouse exceeded the volume of the corresponding tumors transplanted in the standard isolated variant: B16/F10 – by 2.2 times, S45 – by 3.2 times (Table 1).

Table 1. Features of growth of mouse B16/F10 melanoma and rat sarcoma 45 in the MMPT model No. 1 in male mice of the BALB/c Nude line, (M ± m)

Study object	Control 1 (B16/F10), *n* = 7	Control 2 (C45), *n* = 7	MMPT model No. 1, *n* = 7	
			B16/F10	C45
Date of appearance of the tumor, day	11.3 ± 0.6	10.9 ± 0.8	4.3 ± 0.4[1]	5.4 ± 0.6[2]
The volume of the tumor 3 weeks after the transfer, cm^3	1.3 ± 0.1	1.1 ± 0.1	2.9 ± 0.3[1]	3.5 ± 0.3[2]
Life length, days	30.4 ± 2.3	43.0 ± 2.9	22.0 ± 0.6[1,2]	

Note: statistically significant difference is revealed in comparison with [1] – isolated B16/F10 melanoma growth; [2] – isolated sarcoma 45 growth ($p < 0,05$). B16/F10, i.e B16/F10 melanoma, S45, i.e. sarcoma 45.

Table 2. Features of the growth of mouse melanoma B16/F10 and rat GC in the MMPT model No. 2 in female mice of the BALB/c Nude line, (M ± m)

Study object	Control 3 (B16/F10), *n* = 7	Control 4 (GC), *n* = 7	MMPT model No. 2, *n* = 7	
			B16/F10	GC
Date of appearance of the tumor, day	12.3 ± 0.5	7.6 ± 0.4[1]	4.0 ± 0.6[1]	2.7 ± 0.5[2]
The volume of the tumor 2 weeks after the transfer, cm^3	0.2 ± 0.09	3.8 ± 0.2[1]	1.7 ± 0.1[1]	8.4 ± 0.9[2]
Life length, days	33.3 ± 2.4	24.9 ± 1.0[1]	16.6 ± 0.8[1,2]	

Note: statistically significant difference is revealed in comparison with [1] – isolated B16/F10 melanoma growth; [2] – with isolated growth of GC ($p < 0,05$). B16/F10 – melanoma B16/F10, GC is Guerin's carcinoma.

It was found that B16/F10 in MMPT model No. 1, in addition to typical places (lungs, spleen, liver), metastasized to S45 from the side adjacent to the chest – under the capsule of the tumor node.

The life expectancy of the mice depended on the histological type of tumor and the variant of grafting: isolated or combined. Mice with isolated growth of rat S45 lived for the longest time: their minimum life expectancy was 35 days (2 mice, 28.6 %), maximum – 56 days (1 mouse, 14.3 %), average – 43 days (Table 1). Mice with isolated B16/F10 growth lived on average 10 days less than mice with S45, while their minimum life expectancy was 27 days (3 mice, 42.8 %), the maximum was 42 days (1 mouse, 14.3 %). Mice with MMPT model No. 1 lived the least: their average life expectancy was 1.5 times ($p < 0.05$) less than in mice with isolated growth B16/F10, and 2.0 times less than in mice with isolated growth S45 (Table 1); their minimum life expectancy was 21 days (3 mice, 42.8 %), the maximum is 25 days (1 mouse, 14.3 %).

Thus, with successive subcutaneous grafting of mouse B16/F10 and rat S45 to male mice of the BALB/c Nude line, the malignant potential of each of the tumors increased, which manifested itself in shortening the time of their appearance and increasing the rate of tumor growth and contributed to a decrease in the life expectancy of animals with MMPT model No. 1.

When reproducing MMPT model No. 2, the following results were obtained, which are presented in Table 2.

In female mice of the BALB/c Nude line, rat GC, with subcutaneous grafting, appeared on average 5 days earlier ($p < 0.05$) than mouse B16/F10, also grafted under the skin. The period of the appearance of the GC tumor is from 6 to 9 days from the moment of transplantation, B16/F10 from 11 to 15 days. In female mice with sequential grafting of two strains, both tumors appeared almost immediately: GC in the first mouse (14.3 %) the day after grafting, B16 /F10 two days later in 2 mice (28.6 %); the end date of the appearance of GC 4–5 days (1 mouse, 14.3 %), B16/F10 5 (3 mice, 42.8 %) – 6 (1 mouse, 14.3 %) days. The tumor B16/F10 had the appearance of a black millet grain, the tumor GC was a white rounded formation with a diameter of 3.2 ± 0.03 mm. Thus, in MMPT model No. 2, both tumors appeared, on average, three times faster than with isolated grafting, while there was no statistically significant difference in the timing of the appearance of combined tumors (Table 2). The volume of tumors in mice in all groups was measured before the death of the first mice with MMPT model No. 2 on 14 days from the moment of the transfer. Figure 1 shows a photograph of a female with two tumor nodes after successive transplantation of mouse B16/F10 (left) and rat GC (on the right).

The volume of each tumor sequentially transplanted into one mouse exceeded the volume of the corresponding tumors transplanted in an independent variant: the tumor on the left (in the area of B16/F10 grafting) compared with a single tumor B16/F10 7.5 times, the tumor on the right (in the area of GC grafting) compared with a single tumor GC – 2.2 times (Table 2). The subcutaneous tumor located at the site of the B16/F10 grafting had an atypical appearance for melanoma: rounded shape, soft-elastic elastic consistency, light color (with the exception of a small spot, i.e. the grafting point, 3.4 ± 0.2 mm in diameter, which was black in color, and a pronounced venous network on the skin (Fig. 2).

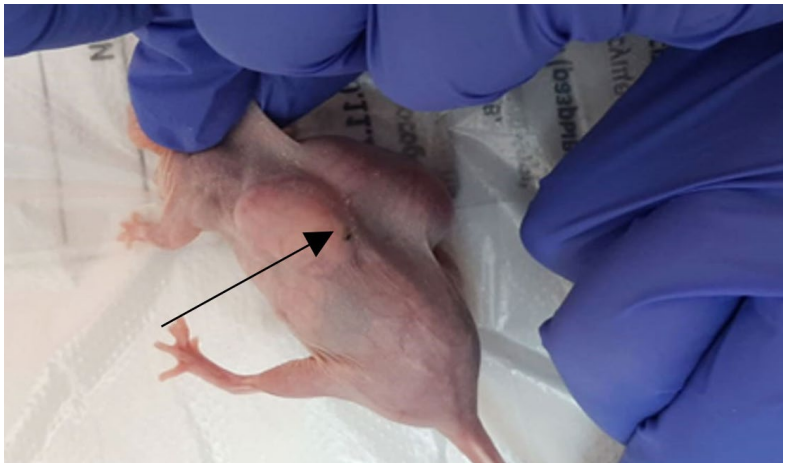

Fig. 1. Type of subcutaneous tumors: melanoma B16/F10 (left) and GC (right) in a female of the BALB/c Nude line in the experimental MMPT model No. 2; a black spot is the place of melanoma grafting (arrow).

Upon autopsy, it was found that GC in all mice metastasized to B16/F10 and almost completely suppressed its growth. Most of the subcutaneous tumor located on the left was occupied by GC tissue. Melanoma B16/F10 was represented by a small "island" of tissue of uneven color, located "on top" of the tumor tissue GC. Immediately under the skin at the injection site of B16/F10 cells, a tumor site with a diameter of 3.3 ± 0.2 mm of black color was visualized. Around the dark "center" there was a light part B16/F10 of the same loose pasty consistency as the dark part, with a diameter of 6.5 ± 0.3 mm. For the rest, the tumor on the left had the appearance of an elongated node of grayish-pink color, dense elastic consistency – just like the tumor on the right, which was much larger in volume. The right and left tumors did not merge with each other, there was a small distance between them of at least 2–3 mm. A small focus of caseous necrosis with a diameter of 6.8 ± 0.2 mm was registered in the center of the right tumor of the GC, there was no necrosis on the left. The smaller size, absence of necrosis, and visually more "young" tissue of the GC on the left testified to its later occurrence than on the right, which, combined with the remnants of B16/F10 soldered to the left tumor, indicated the metastatic nature of the tissue of the GC on the left. B16/F10 did not metastasize even to typical sites, including lungs. The rounded formation under the skin, located below the left tumor, turned out to be the end of the sternum, deployed by the right tumor node.

The life expectancy of female mice with MMPT model No. 2 was minimal, a little more than 2 weeks (Table 2). Female mice with isolated GC growth lived a week longer. The life expectancy of female mice with B16/F10 turned out to be maximum, more than 4 weeks (Table 2).

Thus, successive subcutaneous inoculation of mouse B16/F10 and rat GC to female mice of the BALB/c Nude line contributed to the suppression of tumor growth of B16/F10 and increased the malignant potential of GC.

CONCLUSION

Summarizing the results obtained from the developed and studied experimental MMPT model No. 1 and MMPT model No. 2 in animals with congenital, genetically determined immunodeficiency, it can be concluded that with successive grafting of heterogeneous tumor material, the "manifests itself" of each tumor depends on the histological structure, and, consequently, the biological activity of both tumors. With different combinations, the same tumor in the MMPT model "behaves" differently. In one case, its aggressiveness may increase (B16/F10 with simultaneous growth with S45 in MMPT model No. 1 in males), which manifests itself not only in an increase in its growth rate, but also in active metastasis, including to another tumor (S45). In another case, its growth is almost completely suppressed by the second tumor (B16/F10 with simultaneous growth with GC in MMPT model No. 2 in females).

In general, successive subcutaneous inoculation of mouse B16/F10 and rat S45 to male mice of the BALB/c Nude line increased the malignant potential of each tumor: the period of their appearance accelerated and the rate of tumor growth increased, which contributed to a decrease in the life expectancy of animals. Successive subcutaneous inoculation of mouse B16/F10 and rat GC to female BALB/c Nude mice contributed to the suppression of tumor growth in B16/F10 and increased the malignant potential of GC.

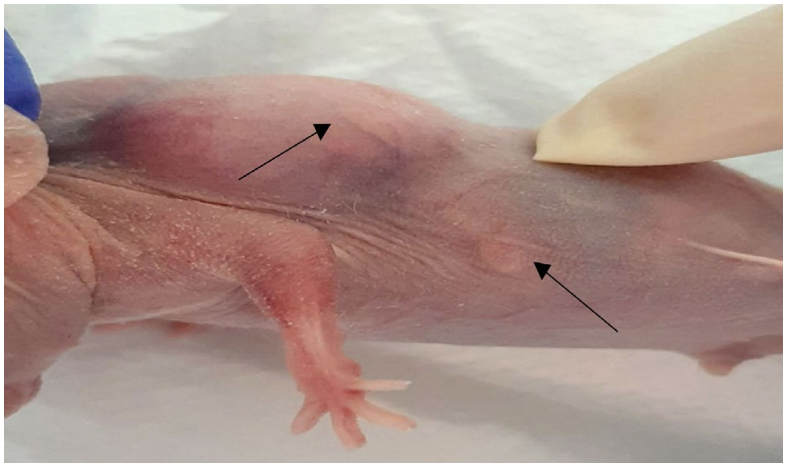

Fig. 2. View of the subcutaneous tumor located on the left – the side of the melanoma B16/F10 grafting in a female of the BALB/c Nude line in the MMPT model No. 2, with a pronounced venous network (arrow); below the tumor is a rounded cartilaginous formation with a diameter of about 5–6 mm.

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Information about authors:

Elena M. Franzyants – Dr. Sci. (Biol.), professor, deputy general director for science, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0003-3618-6890, SPIN: 9427-9928, AuthorID: 462868, ResearcherID: Y-1491-2018, Scopus Author ID: 55890047700

Irina V. Kaplieva – Dr. Sci. (Med.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-3972-2452, SPIN: 5047-1541, AuthorID: 734116

Valeriya A. Bandovkina – Dr. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-2302-8271, SPIN: 8806-2641, AuthorID: 696989

Ekaterina I. Surikova – Cand. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-4318-7587, SPIN: 2401-4115, AuthorID: 301537

Irina V. Neskubina – Cand. Sci. (Biol.), senior researcher at the laboratory for the study of the pathogenesis of malignant tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-7395-3086, SPIN: 3581-8531, AuthorID: 794688

Lidiya K. Trepitaki – assistant researcher at the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-9749-2747, SPIN: 2052-1248, AuthorID: 734359

Yuliya A. Pogorelova – Cand. Sci. (Biol.), senior researcher at Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-2674-9832, SPIN: 2168-8737, AuthorID: 558241

Natalya D. Cheryarina – laboratory assistant at the laboratory for the study of the pathogenesis of malignant tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-3711-8155, SPIN: 2189-3404, AuthorID: 558243

Elena A. Sheiko ✉ – Cand. Sci. (Biol.), junior research fellow of the laboratory of Malignant Tumor Pathogenesis Study National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-9616-8996, SPIN: 7293-3480, AuthorID: 479978

Inga M. Kotieva – Dr. Sci. (Med.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-0252-4708, SPIN: 3478-5811, AuthorID: 637665

Konstantin A. Shumarin – PhD student of the National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-4362-9303, SPIN: 5042-4897, AuthorID: 1090463

Contribution of the authors:

Frantsyants E. M. – research concept and design, text writing, data analysis and interpretation;
Kaplieva I. V. – research concept and design;
Bandovkina V. A. – assistance in operations;
Surikova E. I. – technical editing, material processing;
Neskubina I. V. – scientific editing;
Trepitaki L. K. – assistance in operations;
Pogorelova Yu. A. – assistance in operations;
Cheryarina N. D. – technical editing, material processing;
Sheiko E. A. – technical editing;
Kotieva I. M. – scientific editing;
Shumarin K. A. – collection, analysis and interpretation of data.