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Changes in the number and morphology of blood cells in mice pretreated with RNA preparations and exposed to 8 Gy of gamma radiation

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ABSTRACT

***Background*:** In our recent studies, yeast double-stranded RNA showed radioprotective effect in mice exposed to 9.4 Gy of gamma radiation. The current work continues our inquiry and describes the changes in the number and morphology of blood cells in mice injected with double-stranded RNA from *Saccharomyces cerevisiae* prior to gamma irradiation. To be capable of estimating the required parameters, we have used 8 Gy of radiation, which allowed mice to survive for up to 37 days (LD60/30). ***Materials and Methods*:** Animals received single intravenous injections of one of the following compounds: (1) 7 mg of total RNA isolated from baking yeast *Saccharomyces cerevisiae*, (2) 200 μg of double-stranded RNA or (3) 400 μg of double-stranded RNA. 30 minutes later, using a ^{137}Cs gamma emitter, mice were irradiated with a dose of 8 Gy at the rate of 1.4 Gy/min. The radioprotective effect of preparations was assessed based on death rates. ***Results*:** Injections of both 200 μg of double-stranded RNA and 7 mg of total RNA prior to irradiation provided the best radioprotective effects, ensuring the survival of 100% of animals. Changes in the number of blood cells and their morphological aberrations were being monitored for 37 days after irradiation. ***Conclusion*:** The protection from lethal radiation doses is associated with the preservation and rapid recovery of leukocytic and erythroid lineages.

INTRODUCTION

Radioprotectors, both novel and employed in various branches of industry, are described in numerous reviews, handbooks, and manuals [1–3]. Nevertheless, the search for an efficient, relatively cheap and low- or non-toxic drug mitigating all manifestations of the acute radiation syndrome is still a challenge [4–6].

The acute radiation syndrome (ARS) develops as pathological changes in a number of functional systems. Depending on the irradiation dose, changes occur in the hematopoietic system, gastrointestinal tract, reproductive system, skin and neurovascular system of mammals [1,2,7]. The hematopoietic system is known to be the most susceptible to gamma radiation that damages all hematopoietic lineages, as seen from the reduced number of blood cells [8–10]. Among other consequences of irradiation are hemorrhages, including those due to radiation-induced blood-clotting disorders. Generally, ARS is accompanied by hemorrhages, blood effusions, microvascular thrombosis as well as organ injuries resulting in death from multiple organ failure (disseminated intravascular coagulopathy) [11]. Another characteristic manifestation of irradiation is associated with numerous pathomorphological aberrations in blood cells of all major hematopoietic lineages [12–15].

One of the main radioprotective mechanisms is the preservation of hematopoietic progenitors, which can be determined upon examination of both bone marrow and peripheral blood cells. Restoration of both the number and composition of white and red blood cells, as well as their progenitors, implies the recovery of hematopoiesis corrupted by irradiation.

In our recent studies [16,17], yeast double-stranded RNA (dsRNA) showed pronounced radioprotective and moderate radiotherapeutic effects on deadly (9.4 Gy) irradiated mice. It was shown that the protection

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of animals against lethal irradiation was associated with the preservation of CD34+ hematopoietic stem cells, their migration to peripheral lymphoid organs (spleen) and the formation of new nodes with actively proliferating immune cells. Analysis of bone marrow cells and splenic colonies showed that the treatment with *Saccharomyces cerevisiae* RNA is accompanied by the preservation of both leukocytic and erythroid lineages [17].

The present work continues our inquiry mentioned above. The mail goal of our study was to assess the potential of *S. cerevisiae* RNA in preserving hematopoietic lineages upon irradiation. We have also aimed to compile a mini-atlas of comparative pathomorphological changes in blood cells of irradiated animals, both treated and untreated with *S. cerevisiae* RNA. For this purpose, we have analyzed the changes in the number and morphology of blood cells in mice exposed to 8 Gy of gamma radiation (LD60/30): control and pretreated with RNA from *S. cerevisiae* yeasts.

MATERIALS AND METHODS

Animals

Experiments were conducted using 3-month old C57BL/6 mice (females, 18-22 g) bred at the Institute of Cytology and Genetics, SB RAS. Animals were grown in groups of 6-10 mice per cage with free access to food and water. All experiments with animals were conducted in strict compliance with the principles of humanity in accordance with the European Community Council Directives (86/609/EEC) and were approved by the Animal Care and Use Committee of the Institute of Cytology and Genetics SB RAS (protocol N 8 from 19 March 2019).

Irradiation

Mice were irradiated using a ^{137}Cs gamma emitter, (IGUR 1, Russia) with a dose of 8 Gy at the rate of 1.4 Gy/min. Based on the previous experience, we have tried to achieve LD50/30 as this is a commonly used dose to study the bone marrow syndrome in mice [18]. Experimental and control animals were irradiated in groups of 5-7 animals in a 20×20×40-cm box. The radioprotective effect of the preparation was assessed based on animal mortality.

RNA preparations

Total yeast RNA was purchased from Biolar Company, Russia. dsRNA was obtained by the hydroxyapatite chromatographic fractionation of total yeast RNA under standard condition as described in [17].

Experimental design

It was planned to take blood samples from each animal daily for 37 days. Therefore, experimental groups were small: n = 5 to 7. Analysis of the survival in the groups was not the study objective and was done merely as an additional assessment, and the results were consistent with earlier experiments.

The used radiation dose of 8 Gy allowed the irradiated mice to survive for 37 days, which were sufficient for monitoring the changes in blood of both control and experimental animals, while the dose of 9.4 Gy resulted in quick (14-17 days) lethal outcome in control animals.

30 minutes before irradiation, animals received a single injection of either 7 mg of total RNA (ΣRNA) or 200 or 400 μg of dsRNA into the caudal vein (n = 7 in each group). Control animals (n = 5) received saline. Injection volume was 400 μl. Blood parameters were monitored in 3 animals from each group. Blood sampled from the caudal vein was used for preparing smears and subsequent determining the leukocytic formula. The zero point samples were taken before RNA administration.

Hematological assay of irradiated mice

Blood smears were fixed with methanol (JSC "Vekton", Russia) for 6–10 min, washed with water, dried, and stained according to Giemsa-Romanovsky, pH 7.4. Slides were examined using Leica DV 4000V microscope (Germany) in transmitting light with immersion, magnification ×100.

Since the volume of blood samples, which could be taken from the caudal vein, was insufficient for the complete blood analysis, particularly for exact counting the number of cells per mL, some non-conventional methods were engaged. The relative number of leukocytes (RNL), calculated as the ratio of the leukocytes number (Nl_t) to that of erythrocytes (Ne_t), was determined for each sample. Further, these relative numbers determined for the experimental points were expressed as a percentage of the initial one (Nl_0/Ne_0, referred to as 100%) using the following formula: $RNL_t(\%)=(Nl_t/Ne_t)/(Nl_0/Ne_0) \times 100$.

Assessment of dsRNA mutagenicity

The mutagenic potency of dsRNA was assessed by analyzing chromosomal aberrations in bone marrow cells 24 hours after intraperitoneal administration of 100 μg of the preparation per mouse. Five animals were tested in both control and experimental group. One hundred metaphases were examined for each animal. The significance of difference ($p<0.01$) between the groups was assessed by Mann-Whitney U-test.

RESULTS

Survival assessment and analysis of blood cell number in mice treated with RNA and exposed to 8 Gy of gamma radiation

Since the mortality of mice exposed to 9.4 Gy occurred within 14-17 days, we have chosen a dose of

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8 Gy allowing irradiated mice to survive for 37 days (LD60/30), during which we compared the gradual changes in blood cells number and morphology.

Mortality of mice irradiated with 8 Gy is plotted in figure 1A. The survival rate of animals having received ΣRNA or 200 μg of dsRNA was 100%. The survival rate of mice having received 400 μg of dsRNA was 85.7%. In the control group, 40% of mice survived. The rate and reliability of blood composition recovery after irradiation strongly correlated with the survival in the groups: the best results were observed in the groups pretreated with either ΣRNA or 200 μg of dsRNA (figure 1). Below, we also provide a general comparative description of changes in the populations of blood cells during the 37 days of monitoring.

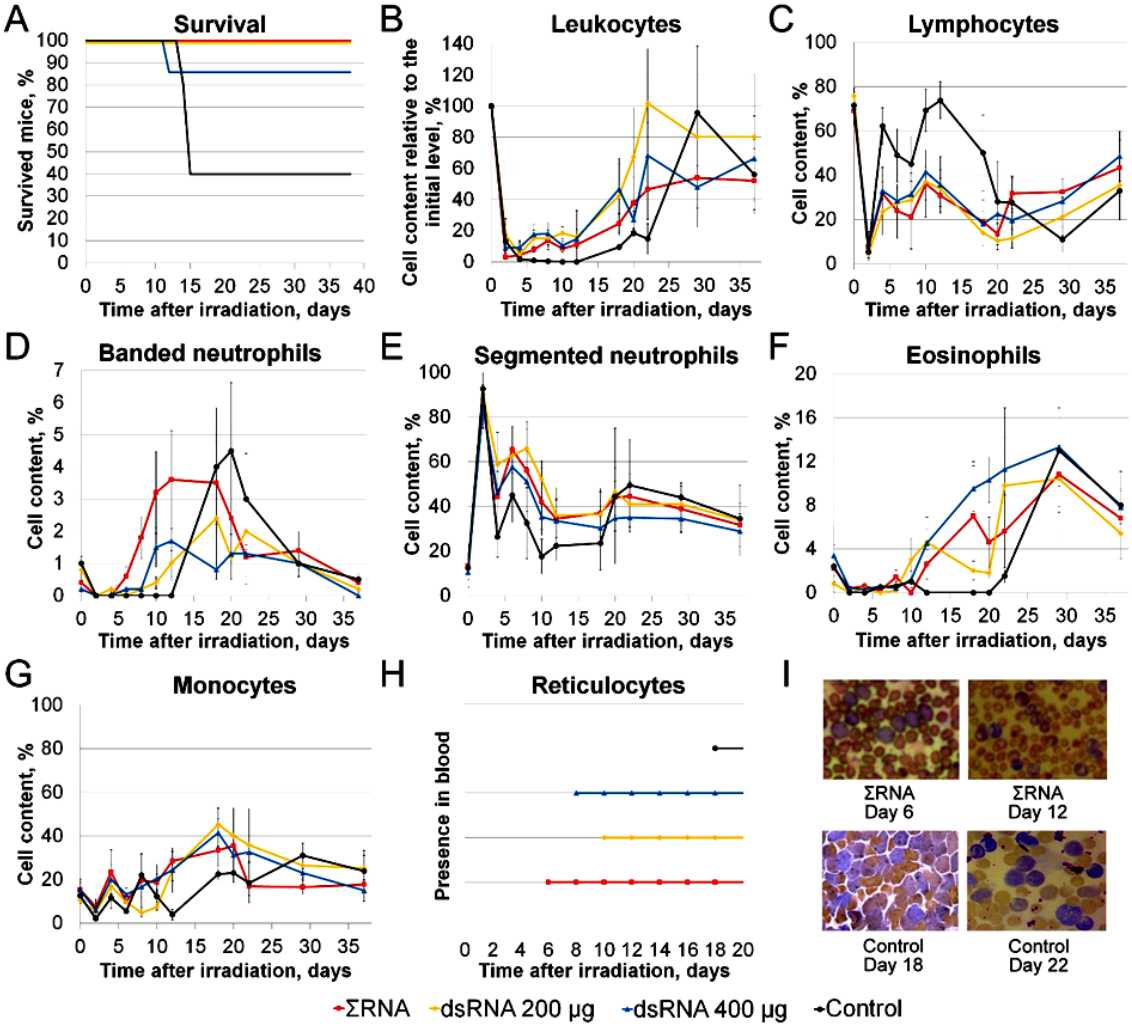


Figure 1. The survival of animals **(A)** and time variations of number of leukocytes **(B)** and blood cells – lymphocytes **(C)**, banded neutrophils **(D)**, segmented neutrophils **(E)**, eosinophils **(F)**, and monocytes **(G)** in the control group and in groups having received 7 mg of ΣRNA, 200 μg of dsRNA, or 400 μg of dsRNA 30 min prior to irradiation. The values are means±SD. **H** – time of reticulocyte appearance in blood of all animals from the appropriate groups. **I** – reticulocytes in blood.

Leukocytes

The most drastic changes were observed in the leukocytic fraction. All irradiated animals showed severe leukopenia on day 2 after irradiation (figure 1B). In the control group, almost complete depletion of leukocytes was observed for 12 days. In groups pretreated with ΣRNA or dsRNA, leukocyte populations began to restore on days 6–8 after irradiation (figure 1B). Neither of the observed animals displayed a complete restoration of leukocytic fraction after 37 days of monitoring.

Lymphocytes

In full accordance with the day 2 leukopenia, all irradiated animals suffered of a sharp drop in the number of lymphocytes on day 2 after irradiation (figure 1C). In the control group, an abrupt increase in this index was observed on day 4, and it lasted till day 12. Then, starting from day 18, the number of lymphocytes decreased monotonously and remained extremely low till the end of observation. In the experimental groups, lymphocyte decrease was detected on days 18–22, after which their population restored gradually till the end of the experiment.

Neutrophils

The numbers of *band neutrophils* fell to zero within the first 48 h after irradiation in all groups

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(figure 1D). In the control group, an abrupt increase in the band population was recorded as late as day 18, a followed by the decrease to the normal value by the end of observation. In the experimental groups, this index began to restore on day 6-8, remained high till days 18-22, and returned to the normal value by the end of observation.

The numbers of *neutrophils with segmented nuclei* abruptly increased on day 6 after irradiation in all groups (figure 1E). Pronounced neutrophilia was observed till the end of observation.

The numbers of *eosinophils* decreased immediately after irradiation (figure 1F). In the control group, the number of eosinophils began to increase only on day 22. In the experimental groups, the numbers of eosinophils increased abruptly on days 10–12. In the 200-μg group, a transient decrease in their population was recorded on days 18–20, and then the population rose dramatically again. Pronounced eosinophilia was observed in all groups at the end of observation.

Monocytes

In all irradiated animals, the number of monocytes decreased significantly on day 2 after irradiation and then oscillated within a broad range for 18 days (figure 1C). 22 days later and until the end of monitoring, it stably exceeded the baseline.

Cells of erythroid lineage

The restoration of the erythropoietic lineage was featured by the appearance of numerous reticulocytes, which were first detected 6 days after irradiation in the ΣRNA group and on days 8 and 10 in the remaining 400 and 200-μg dsRNA groups, respectively (figure 1H, 1), which, in turn, correlated with high survival in these groups. In the control group, reticulocytes appeared only on day 18 after irradiation, demonstrating at least a 10-day retardation relative to the pretreated animals.

Morphological aberrations in blood cells

For every type of cells, all the pathomorphological changes found were described, and the corresponding images were composed into particular groups (by similarity) and presented as a brief atlas of cellular abnormalities, subdivided into three parts: 1) abnormalities in the leukocytic/erythroid lineage; 2) apoptotic/necrotic cells; 3) abnormalities in cell morphology and atypical blood cells. Additionally, images of myelo-/erythropoietic cells demonstrating the recovery of hematopoiesis are provided. Table 1 shows data on the content (%) of aberrant and/or atypical cells along the monitoring period in both control and experimental animals.

Table 1. Mean percentage of aberrant or atypical cells in the blood of irradiated animals.

Cell types	Group	Days after irradiation										
		2	4	6	8	10	12	18	20	22	29	37
Lymphocytes with small grains	ΣRNA	13.2	11.3	10.9	12.3	-	3.9	2.6	4.5	-	3.7	1.4
	200 mkg dsRNA	16.0	7.6	-	1.4	4.3	-	-	-	-	15.1	3.4
	400 mkg dsRNA	17.0	6.0	7.0	7.0	13.9	11.2	-	1.9	6.7	4.7	0.6
	Control	14.8	5.1	1.5	6.7	-	-	-	-	-	4.4	1.2
Lymphocytes with large grains	ΣRNA	-	2.5	-	-	-	2.6	-	-	-	-	-
	200 mkg dsRNA	-	5.1	-	-	1.1	14.7	-	-	-	-	-
	400 mkg dsRNA	-	3.8	2.1	-	2.4	-	-	-	-	-	-
	Control	-	-	-	-	-	-	-	-	-	-	-
Lymphocytes with micronuclei	ΣRNA	-	-	1.7	4.7	0.6	-	1.3	3.0	-	0.6	-
	200 mkg dsRNA	-	-	1.8	2.1	-	-	-	1.9	-	0.9	-
	400 mkg dsRNA	-	-	-	0.6	3.0	2.8	1.4	5.8	1.7	-	-
	Control	-	-	-	1.3	0.4	-	-	-	-	-	-
Binucleate lymphocytes	ΣRNA	5.3	2.5	-	-	2.8	-	-	3.0	-	-	-
	200 mkg dsRNA	-	-	-	-	-	-	-	-	-	-	-
	400 mkg dsRNA	-	-	-	-	-	-	-	-	-	-	1.1
	Control	-	-	-	-	-	-	-	-	-	-	-
Anisocytes	ΣRNA	-	3.8	5.0	3.8	0.6	-	-	-	-	-	-
	200 mkg dsRNA	-	-	-	-	-	-	-	-	-	-	-
	400 mkg dsRNA	-	-	-	-	0.6	-	-	-	-	-	-
	Control	-	11.9	2.6	2.7	-	-	-	-	-	-	-
Hyperseg-mented granulocytes	ΣRNA	0.5	3.6	0.6	3.6	-	0.6	-	-	-	-	-
	200 mkg dsRNA	0.4	-	-	-	-	-	-	-	-	-	-
	400 mkg dsRNA	1.3	0.5	-	-	-	-	-	-	-	-	-
	Control	-	-	-	-	-	-	-	-	-	-	-
Macrophages	ΣRNA	-	-	12.0	11.2	6.6	2.1	4.5	-	-	-	1.1
	200 mkg dsRNA	-	10.5	7.7	4.2	-	4.1	0.4	-	2.2	6.4	3.2
	400 mkg dsRNA	-	4.9	4.6	6.0	2.4	10.0	-	5.0	1.7	-	-
	Control	-	8.6	18.2	14.6	15.0	-	-	-	-	-	2.9
Juvenile cells	ΣRNA	-	-	-	1.9	3.7	6.4	2.2	3.4	-	-	-
	200 mkg dsRNA	-	-	-	-	3.0	4.3	-	7.7	3.4	-	-
	400 mkg dsRNA	-	-	1.0	0.6	2.4	4.2	0.9	0.9	-	1.9	0.8
	Control	-	-	-	-	-	-	-	-	-	-	-
Apoptotic cells	ΣRNA	-	0.8	-	1.0	-	-	-	-	-	-	-
	200 mkg dsRNA	-	-	-	-	-	-	-	-	-	-	-
	400 mkg dsRNA	0.6	-	-	-	-	-	-	-	-	-	-
	контроль	-	10.0	3.3	3.3	5.5	4.0	-	-	-	-	-

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Abnormalities in leukocytic lineage

Mononuclear cells with granular and vacuolated cytoplasm appeared in blood smears on the next day after irradiation (figure 2A1, 2). The granular mononuclears may be a fraction of natural killers, and the increase in their population may be associated with their role in the lysis of damaged cells, abundant after irradiation. In some cases, granules detected in mononuclear cells were so large that they looked like exogenous inclusions in the cytoplasm (figure 2A2). Many lymphocytes were adhered to pericytial debris (figure 2A3). Also, there were unviable lymphocytes with a wide pale band of the cytoplasm (figure 2A4). Cytoplasmic and nuclear bulges, which indicated the initial stages of cell death, were the most typical abnormalities for mononuclear cells (figure 2A5, 6).

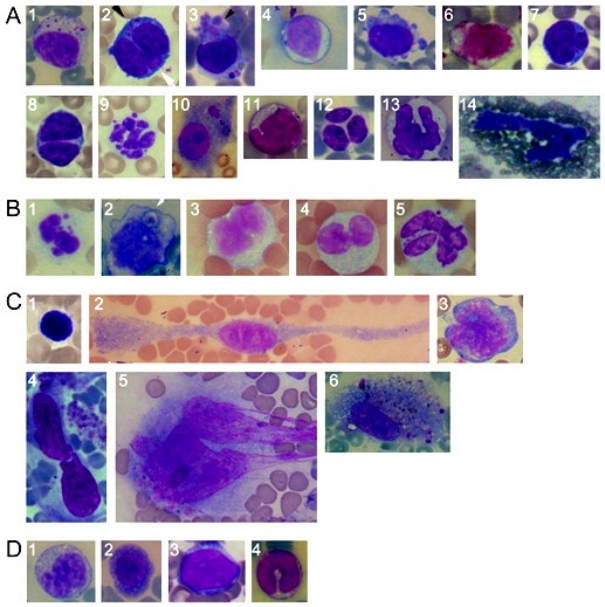


Figure 2. A – Abnormalities in the leukocytic and erythroid lineages. **1 –** granular lymphocyte; **2 –** mononuclear with inclusions in cytoplasm (white arrows indicate large inclusions; black arrow, small); **3 –** lymphocyte adhered to debris; **4 –** cell with a wide pale band of the cytoplasm; **5 –** cell with cytoplasmic bulges; **6 –** cell with nuclear bulges; **7 –** mononuclear cell with micronuclei; **8 –** binucleated mononuclear cell; **9 –** neutrophil with very small dust-like segments; **10 –** binucleated cell with numerous inclusions; **11 –** cell with notched nucleus; **12 –** nucleus hyposegmentation in neutrophil; **13 –** monocyte with shaped nucleus; **14 –** blood clot with platelets. **B – A**poptotic/ necrotic cells. **1 –** apoptotic lymphocyte; **2 –** cell with inclusions (thin arrow); **3 –** monocyte with vacuoles in cytoplasm; **4 –** a monocyte with clump-like nuclei and signs of apoptosis; **5 –** abnormal granulocyte. **C –** Abnormalities in cell morphology and atypical blood cells. **1 –** lymphocyte anisocytosis; **2 –** huge fusiform cell; **3 –** large unidentified cell; **4 –** very large cell difficult to be assigned to any type of blood or marrow cells from their morphology; **5 –** megakaryocyte; **6 –** very large macrophage with signs of the active state: numerous vacuoles and debris remnants in cytoplasm. **D –** Myelo- and erythropoiesis. **1 –** metamyelocyte; **2 –** oxyphilic normocyte; **3 –** large lymphocyte with darkened cytoplasm; **4 –** early eosinophil.

Within the first day after irradiation, we observed cells with micronuclei, sometimes very large, and pseudobinucleated cells (figure 2A7). There were also true binucleated lymphocytes (figure 2A8). The maximum number of micronuclei was recorded on days 6–8, but cells with micronuclei were detected in blood samples from all experimental groups even one month after irradiation. The presence of micronuclei indicates an abnormal mitosis in irradiated cells, and their abundance soon after irradiation is quite expected. At the same time, their presence, albeit in small quantities, after a long time span is surprising. There were both hyper segmented neutrophils and those undergoing the fragmentation (up to pinpoint fragmentation) of nuclei observed. Abnormally shaped neutrophils were also noted (figure 2A9).

As well, there were binucleated cells with numerous inclusions, which resembled either Langhans cells or large macrophages of lung granulomas, showing a similar binuclear morphology (figure 2A10).

On day 18 after irradiation, lymphocytes with abnormally shaped, sometimes notched nuclei have appeared (figure 2A11). There were also numerous weakly granulated eosinophils and neutrophils with abnormal segmentation, namely, hyposegmentation of nuclei with two or three major lobes and unusual segmentation morphology (figure 2A12).

Monocytes also showed morphological abnormalities in nuclei. Small cells with regularly shaped nuclei were predominant in intact animals. After irradiation, oversized cells with huge lobate or segmented nuclei have appeared in all groups (figure 2A13) and persisted up to 37 days of observation. At the later observation period, there are oversized monocytes with large nuclei and vacuolated cytoplasm, morphologically resembling macrophages, appeared. Many monocyte cells contained inclusions resembling either micronuclei or something different. In some cases, such inclusions could be clearly identified as phagocytosed platelets. Aggregations of platelets were often observed nearby a monocyte. In one case, a phagocytosis event was pinpointed.

Abnormality in cells of erythroid lineage

The most significant abnormality in cells of erythroid lineage found in the dsRNA groups late (18 -29 days) after irradiation was elevated coagulation, which was assessed microscopically from the presence of platelet aggregates and irregular distribution of blood cells in the overall picture of the smear (figure 2A14).

Apoptotic/necrotic cells

Immediately after irradiation, a substantial fraction of apoptotic/necrotic cells has been detected in the blood of irradiated animals (figure 2B),

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particularly in the control group, where these cells persisted for 29 days.

Abnormalities in cell morphology and atypical blood cells

One of the earliest detected morphological changes in cells was the lymphocyte anisocytosis observed in all groups (figure 2C1).

Since day 4, abnormally shaped cells not typical in normal blood and resembling reticular ones appeared in the blood of control animals. They were fusiform and sometimes huge (figure 2C2). On day 10, large unusual cells were noted. They were four- or fivefold larger than erythrocytes (figure 2C3). There were also exceptionally large cells that could not be morphologically related to any type of blood or bone marrow cells (figure 2C4). The most unusual phenomenon was a mature megakaryocyte in blood on day 18 after irradiation in an animal of the 200-μg dsRNA group (figure 2C5). Megakaryocytes are precursors of platelets. They are giant cells normally located in the red bone marrow. The observed cell was so large that it is a mystery how it could get to the bloodstream. Earlier, on days 10 and 12 after irradiation, this group showed large unusually shaped cells resembling early megakaryocytes.

In a short time (4-8 days) after irradiation, huge macrophages with signs of being activated (numerous vacuoles and debris remnants in cytoplasm) were found in all groups (figure 2C6). Since the radiation damages all the blood cells, it can be presumed that this phenomenon preserves tissues from necrotic intoxication. Macrophages persisted in blood until day 37 after irradiation.

Myelo- and erythropoiesis

Juvenile precursor cells were detected since days 10–12 (figure 2D). Cells of the granulocyte lineage included myelocytes (even occasional promyelocytes) and metamyelocytes (figure 2D1). The number of banded neutrophils in experimental groups reached its acme on days 12–18 after irradiation (Figure 1D). Juvenile forms of erythrocyte lineage cells; polychromatophilic and oxyphilic normoblasts (figure 2D2), early lymphocytes (figure 2D3), and early eosinophils (figure 2D4) were noted. Among monocytes, juvenile forms were also detected. Juvenile macrophages, with no vacuoles or debris in cytoplasm, appeared in addition to juvenile forms of blood lineages.

Assessment of the mutagenic potency of dsRNA

In addition, dsRNA injections caused chromosome fragmentation in mitosis, indicating the mutagenic capabilities of dsRNA fragments, which were assessed by analyzing chromosomal aberrations in bone marrow cells. Five animals were tested in both control and experimental group. For each animal, one hundred metaphases were examined (figure 3, table 2).

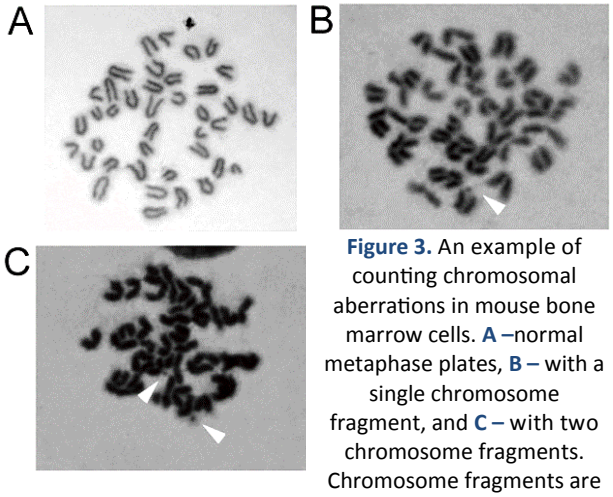


Figure 3. An example of counting chromosomal aberrations in mouse bone marrow cells. **A** –normal metaphase plates, **B** – with a single chromosome fragment, and **C** – with two chromosome fragments. Chromosome fragments are indicated by arrows.

Table 2. Percentages of bone marrow cells with chromosomal aberrations in metaphases in mice having received a single intraperitoneal dsRNA injection and in the control group.

Group	Fragments			Total
	Single	Double	Multiple	
dsRNA 70%	2.75	0.5	1.25	4.5*
Control	1.5-2.0	0	0	1.5-2.0

Note: * Significant difference from the control, $p < 0.01$.

DISCUSSION

Changes observed in the blood of irradiated animals of the control group are generally correspond to those described previously [12,19,20]. The used dose of 8 Gy caused severe leukopenia (excepting segmented neutrophils) within 48 hours, after which lymphocytes decreased by ~90%, and banded neutrophils by almost 100%. In parallel, there was a functional failure of erythroid cells. Restoration of hematopoiesis was detected only by the 18th day. In the groups treated with RNA, such a restoration was observed 10 days earlier. It is the rapid restoration of the hematopoietic function of the bone marrow that determines the high survival in these groups.

In all groups, a variety of atypical blood cells, as well as those with pathological aberrations were observed. The analysis of cell morphology in blood of animals having received dsRNA revealed early progenitors of all three types of leukocytes: lymphocytes, monocytes, and granulocytes. Normally, early progenitors reside in bone marrow niches, and never leave for blood. Thus, the appearance of such cells in the blood is likely due to intense hematopoiesis. The dsRNA groups showed elevated blood coagulation late in the observation, as seen from large platelet aggregations in blood smears.

A notable feature of dsRNA is its mutagenic capability detected both in individual experiments and upon the analysis of pathological changes in cells during their restoration after high radiation doses.

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It is well known that the main factors causing damage to bone marrow cells upon gamma irradiation are the reactive oxygen species appeared mainly as a result of water radiolysis. The most fatal radiation-induced lesions are those of cellular membrane and nuclear genomic DNA. Radioprotective capabilities of the majority of currently used radioprotective compounds, such as indraline and aminothiols [4,5], are based on their capabilities of inducing acute generalized hypoxia in radio-susceptible tissues, primarily in the bone marrow [6]. Other radioprotectors, such as IL-1 [21–23], IL-8 [24,25], thrombospondin- [26,27] and TLR-based preparations [28], are known to preserve the hematopoietic stem cells, and their effect is also associated with the induction of local hypoxia in the bone marrow.

Based on the results we have obtained, it can be presumed that the radioprotective effect of dsRNA has an alternative origin and is associated with its role in facilitating the process of double-stranded brakes repair in bone marrow progenitor cells [17, 29–31], which, in turn, ensures the preservation of hematopoietic progenitors and quick restoration of all stems of hematopoiesis.

CONCLUSIONS

Generally, the radioprotective capabilities of dsRNA against lethal doses are associated with the preservation of hematopoietic progenitors and quick restoration of all stems of hematopoiesis. Moreover, both white and red stems retain their active proliferative status for a long time. Nevertheless, despite the pronounced radioprotective effect, dsRNA does not abrogate pathological aberrations in blood cells.

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Conflicts of interest: *Nothing to declare.*

***Ethical considerations*:** Protocol N 8 from 19 March 2019.

***Author contributions*:** TDD performed the microscopic analysis, GSR carried out experiments with animals, ASP interpreted the data and drafted the manuscript, PEK, VPN and NAP carried out experiments with animals, VSR and OST performed the analysis, NAK participated in the study design, SSB conceived the study and coordinated the manuscript.

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