Volume 19, No 3 | International Journal of Radiation Research, July 2021

Adverse effects of chronic low dose-rate gamma-ray exposure ameliorated by environmental enrichment in mice

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► ***Original article***

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Revised: June 2020
Accepted: July 2020

Int. J. Radiat. Res., July 2021; 19(3): 543-550

DOI: 10.29252/ijrr.19.2.543

ABSTRACT

Background: Chronic long-term irradiation of mice with low dose-rate (20 mGy/day) gamma rays significantly shortened their life spans due to neoplasms and significant suppression of their ability to eliminate transplanted tumors. ***Materials and Methods:*** Mice exposed to chronic 20 mGy/day gamma rays for 400 days and housed in an enriched environment (EE) were compared with those housed in a standard environment. ***Results:*** We demonstrate that an EE significantly ameliorates the suppression of transplanted tumors in mice exposed to chronic low dose-rate gamma rays. Peripheral blood analysis revealed that the proportions of some immune cells were increased by EE housing. Additionally, the number and activity of natural killer (NK) cells in the peripheral blood increased with EE housing, indicating that NK cells may be involved in enhancing the ability to reject transplanted tumors. ***Conclusion:*** To our knowledge, this is the first study to report that the adverse effects, such as the suppression of tumor rejection activity of chronic low dose-rate irradiation exposure, may be alleviated by EE housing, which suggests the possibility that the adverse effects of irradiation may be mitigated by changes in lifestyle.

Keywords: *Environmental enrichment, low dose-rate irradiation, mouse, transplanted tumor.*

INTRODUCTION

High dose-rate radiation and high dose radiation are known to lead to deleterious consequences, including cancers. Recently, interest in the carcinogenic effects of low dose-rate exposure has been increasing in response to occupational exposure, medical exposure, and nuclear power plant accidents such as in Chernobyl and Fukushima. The health effects of exposure to low dose-rate radiation are not well understood and are currently estimated by extrapolating the effects of high dose exposure based on the linear no-threshold model [1-6].

Tanaka *et al.* [7] showed that mice that are chronically exposed to gamma rays at low dose-rates (20 mGy/day) had a statistically significant short life span. Pathological data analysis showed that the short life span was primarily a result of early death from neoplasms [8, 9]. Furthermore, long-term, low dose-rate irradiation in mice has been shown to give rise to obesity [10] and weaken the immune system [11, 12]. These physiological changes may affect antitumor immunity and cause the adverse effects of radiation. To alleviate the adverse effects of radiation, a healthy immune system activity may be necessary. Various methods, such as active and passive immunotherapy, have been developed to increase the antitumor immunity activity *in-vivo* [13].

Recently, an enriched environment (EE) has been reported to decrease tumor size, facilitate

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[DOI: 10.52547/ijrr.19.3.543]

the rejection of transplanted tumor cells [14-19], and prolong the life spans of mice [20]. EE has been defined as the use of housing conditions that enhance the sensory, motor, and cognitive stimulation of brain neuronal systems as compared with the standard caging, and it is also legally required within the European Union by Directive 2010/63/EU [21]. It has been suggested that an EE affects the immune system and activates antitumor immunity through various pathways, resulting in enhanced tumor eradication and extended life span.

To our knowledge, no studies have shown that EE housing has any influence on radiation effects in mice. This report aimed to show whether an EE could alleviate the reduction in tumor rejection activity resulting from exposure to chronic low dose-rate gamma rays. The results of this study suggest the possibility that, even in humans, some lifestyle changes may mitigate the adverse effects of low dose-rate radiation exposure.

MATERIALS AND METHODS

Animals and tumor cell lines

Specific pathogen-free (SPF), six-week-old female B6C3F$_1$ mice were purchased from a commercial breeding facility (Japan CLEA, Tokyo, Japan). After a two-week quarantine and acclimation, the mice were randomly divided into two groups, namely, irradiated (IR group, n = 95) and nonirradiated control (C group, n=102; figure 1A). All of them were housed in an SPF facility maintained at a temperature of 23 °C ±2 °C, with 50% ± 10% humidity, and a 12-h light/dark cycle, and given *ad libitum* access to commercially prepared and gamma-sterilized feed pellets (FR-2; Funabashi Farm Co., Chiba, Japan) and chlorinated drinking water. The mice were housed in groups of four in a plastic cage (TM-TPX-10, 218 W×320 D×133 H mm, floor area of 481 cm^2; Tokiwa Kagaku Kikai Co., Tokyo, Japan) with sawdust bedding.

The tumor cell line OV3121 derived from an ovarian granulosa cell tumor that formed in a female B6C3F1 mouse [22] exposed to ^{60}Co gamma rays at a high dose-rate was purchased from Health Science Research Resources Bank (Osaka, Japan).

The experiments were conducted in accordance with the legal regulations in the Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Guidelines for Animal Experiments of the Institute for Environmental Sciences.

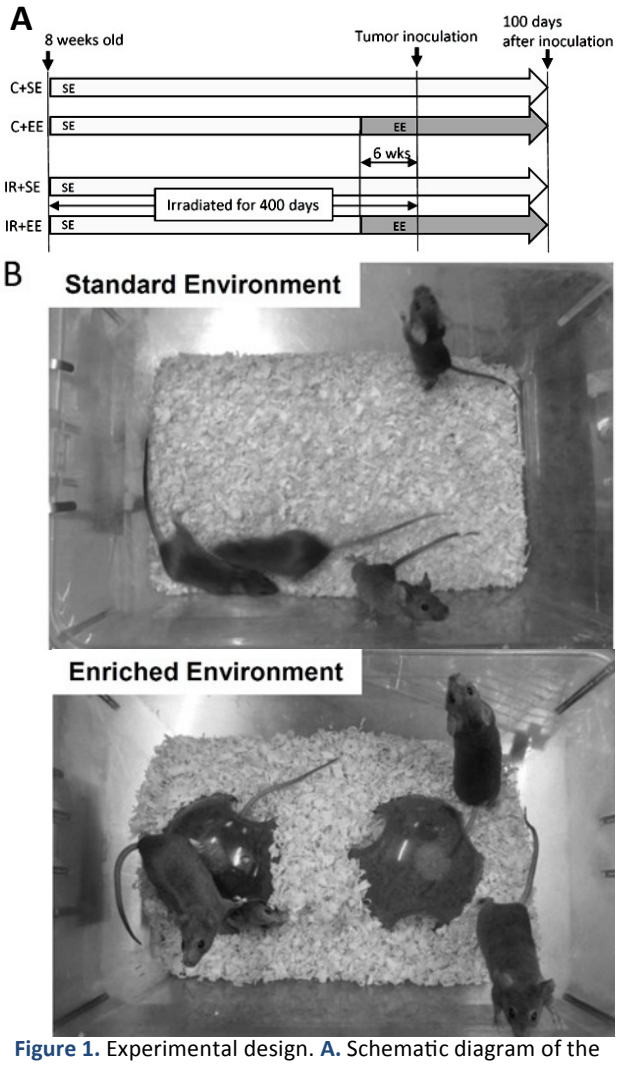


Figure 1. Experimental design. **A.** Schematic diagram of the experimental protocol. **B.** Four mice were housed in a cage of the standard (left) and enriched environments with two igloos (right).

Irradiation

The eight-week-old mice in the IR group were continuously irradiated with ^{137}Cs gamma rays at a low dose-rate of 20 mGy for 22 h a day (74

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GBq, TYR-1501, Yoshizawa LA Co. Ltd., Chiba, Japan) for 400 days. The dose rate was measured using a glass dosimeter (GD-302M, AGC Techno Glass Co., Ltd., Shizuoka, Japan) and a reader (Dose Ace FGD-1000, AGC Techno Glass Co., Ltd.). The mice were transferred to the animal rooms after 400 days of irradiation with a total dose of 8,000 mGy (figure 1A).

Environmental enrichment

To environmentally enrich the standard housing, two mouse igloos (BioServ, Flemington, NJ) were added to each cage for half of the mice in the IR (IR+EE group, n=48) and C (C+EE group, n = 52) group (figure 1B) at six weeks prior to tumor cell inoculation. Every week, the igloos were replaced with clean units. Mice (IR+SE group, n=47 and C+SE group, n=50) in SE housing remained in the same cages. Dose rate differences in EE devices were measured by placing a glass dosimeter inside and outside the igloos.

Tumor cell transplantation

Cultured OV3121 cells were trypsinized and suspended in normal saline to obtain cell suspensions of 1×10^6 cells/ml. Cell suspensions (0.1 ml including 1×10^5 cells) were subcutaneously inoculated into the backs of the mice. Twice a week, the mice were examined by manual palpation for tumor formation and development. The number of tumor-bearing mice (with palpable tumors) detected during the 100-day observation period after inoculation was counted.

Cytotoxic activity of natural killer (NK) cells

After the mice were euthanized with CO_2, whole blood and spleens were collected aseptically. Erythrocytes were lysed using BD PharmLys (BD Biosciences, San Jose, CA). Lymphocytes were then collected. Yac-1 cells (DS Pharma Biomedical Co., Ltd, Osaka, Japan) were labeled using bromodeoxyuridine as described in the manual for Cellular DNA Fragmentation ELISA (Merck KGaA, Darmstadt, Germany) and co-cultured with lymphocytes for 4 h; then, supernatants were collected for analyses. Cytotoxic activities were analyzed in accordance with the procedure for measuring cell-mediated cytotoxicity from Cellular DNA Fragmentation ELISA.

Flow cytometric analysis

Lymphocytes were stained with 7-aminoactinomycin D (7-AAD) and antibodies of fluorescein isothiocyanate conjugated anti-mouse cluster of differentiation (CD) 335, phycoerythrin (PE) conjugated anti-mouse F4/80, PE–cyanine (Cy) 7 conjugated anti-mouse CD8a, PE-Cy5 conjugated anti-mouse CD4, allophycocyanin (APC) conjugated anti-mouse CD11c, APC-Cy7 conjugated anti-mouse CD11b, and PE–Texas red conjugated anti-mouse CD45R (BD Biosciences). FACS Fusion™ (BD Biosciences) was used to calculate cell proportions as 7-AAD-negative and antibody-positive cells.

Statistical analysis

Differences in tumor cell rejection activity between mice housed in EE and SE were examined using the log-rank test. Body weight, cytotoxic activity, and cell proportion were examined using the Tukey–Kramer test. *P* less than 0.05 was considered statistically significant.

RESULTS

Blood samples and spleens were obtained from four mice in each group (C + SE, C + EE, IR + SE, and IR+EE) after completing radiation exposure (or six weeks after installing the igloos in the EE groups) prior to tumor inoculation. All the remaining mice (C+SE, n=46; C+EE, n=48; IR+SE, n=43; IR+EE, n=44) were inoculated with tumor cells and monitored for tumor formation for 100 days after inoculation.

After irradiation, the average body weights of mice were 46.07±7.00 g (C+SE, n=50), 43.17±7.69 g (C+EE, n=52), 49.64±4.06 g (IR+SE, n=47), and 47.74±4.97 g (IR+EE, n=48). Body weights were significantly increased in mice with irradiation (C+SE vs. IR+SE, $p<0.01$; C+EE vs. IR+EE, $p<0.01$) and tended to decrease in mice housed in an EE (figure 2A). Although there

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was a tendency for an earlier occurrence of palpable tumors after tumor cell inoculation in heavier mice, no significant correlation was observed (figure 2B, r^2=0.073).

Peripheral blood analysis using flow cytometry (figure 3A) revealed that proportions of CD11c$^+$, CD45R$^+$, and F4/80$^+$ cells were considerably increased by EE housing (C+SE vs. C+EE and IR+SE vs. IR+EE) and tended to increase with radiation exposure (C+SE vs. IR+SE and C+EE vs. IR+EE). The proportion of CD335$^+$ cells exhibited a tendency to increase in EE housing (C+SE vs. C+EE and IR+SE vs. IR+EE) but significantly decreased with radiation exposure (C+SE vs. IR+SE and C+EE vs. IR+EE).

In the spleen (figure 3B), proportions of CD11c$^+$, CD45R$^+$, and F4/80$^+$ cells were significantly increased by EE housing (C+SE vs. C+EE and IR+SE vs. IR+EE). Proportions of CD335$^+$ cells were significantly increased by EE housing (C+SE vs. C+EE and IR+SE vs. IR+EE) and decreased by radiation exposure (C+EE vs. IR+EE).

Cytotoxic activities of NK cells in these mice were examined by lysing the target Yac-1 cells. In peripheral lymphocytes, activities tended to abate after chronic low dose-rate radiation (C+SE vs. IR+SE and C+EE vs. IR+EE; figure 3A). Similar to changes in the proportion of CD335$^+$ cells, decreased cytotoxic activity after radiation exposure may be improved by EE housing. However, the effects of EE on the cytotoxic activity of NK cells in the spleen did not follow a pattern (figure 3B) similar to that of peripheral lymphocytes.

All the other mice (C+SE, n=46; C+EE, n=48; IR+SE, n=43; IR+EE, n=44) were inoculated with 1×10^5 OV3121 cells and inspected for tumor formation (figure 4). Chronic low dose-rate gamma-ray exposure significantly suppressed the antitumor activity (p<0.001 [C+SE vs. IR+SE and C+EE vs. IR+EE] in the log-rank test). Decreased antitumor activity was significantly alleviated in mice housed in an EE (p=0.028, C+SE vs. C+EE in the log-rank test), even after the onset of gamma-ray exposure (p=0.032, IR+SE vs. IR+EE in the log-rank test). Tumor induction between the IR+EE and C+SE groups was not significantly different (p=0.099).

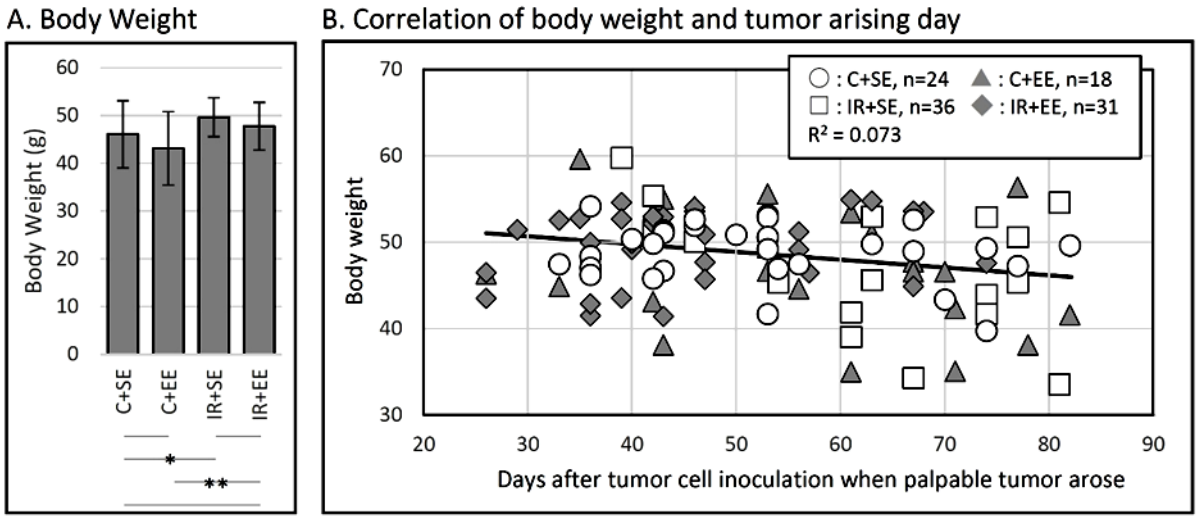


Figure 2. A. The average body weight of mice in each group (C + SE, n = 50; C + EE, n = 52; IR + SE, n = 47; IR + EE, n = 48). **B.** Correlation between body weight during tumor cell inoculation and the day of tumor occurrence. Bar, standard deviation; *, P < 0.05; **, P < 0.01 (t-test).

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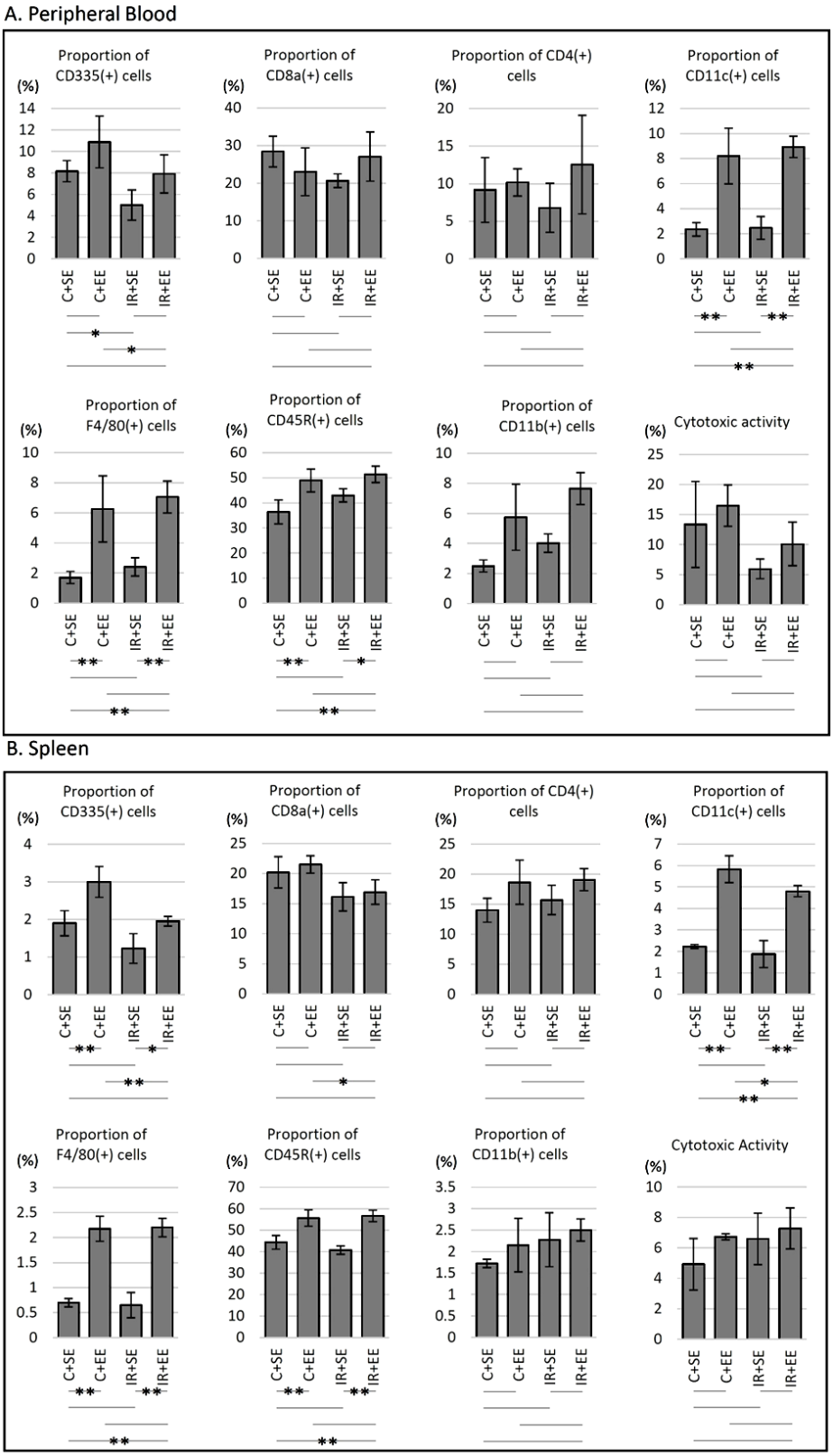


Figure 3. Results of flow cytometric analysis showing proportions of CD335-, CD8a-, CD4-, CD11c-, F4/80-, CD45R-, and CD11b-positive cells and results of NK cell activity in **(A)** the peripheral blood and **(B)** spleen of each group (n = 4, respectively). Bar, standard deviation; *, $P < 0.05$; **, $P < 0.01$ (t-test).

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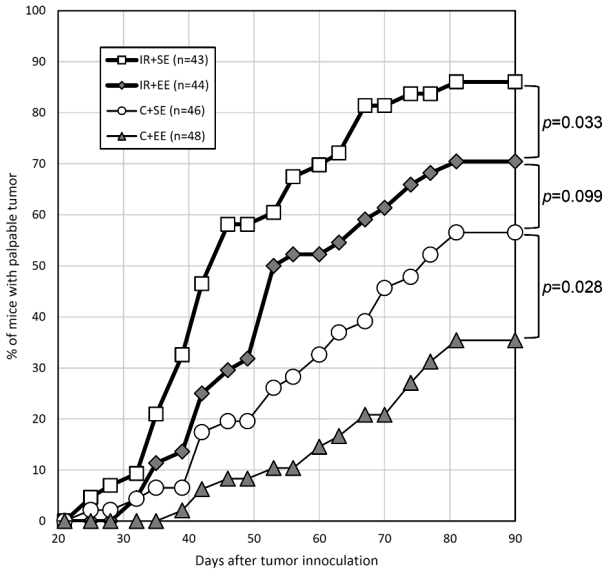


Figure 4. Comparison of transplanted tumor cell rejection activity. P-values were calculated using the log-rank test.

DISCUSSION

To the best of our knowledge, this is the first study to report the possibility that after low dose-rate irradiation, some lifestyle modifications may mitigate the adverse effects of irradiation. This report provides important tips for mitigating the adverse effects of low dose-rate radiation that people who are inevitably exposed to it may experience such as nuclear workers and residents near nuclear power plants.

A previous report [19] demonstrated that the addition of one igloo can adequately enhance tumor rejection. However, one igloo did not have any effect on tumor suppression when mice aged over 400 days were used in the experiment. Based on the body weights of mice at 456 days (>40 g, figure 2A), four mice in one cage were presumed to be too big/heavy to fit in one igloo; hence, in this study, two igloos were installed in each cage (figure 1B) to provide enough space for all the mice.

The dose rate in an igloo was approximately 3% lower than that of the outside. Igloos were installed for six weeks, resulting in a lower total dose in IR + EE (approximately 7,975 mGy) than that in IR + SE (8,000 mGy) groups. The 25 mGy difference was considered small and could be disregarded.

As in previous reports [7, 8, 10], chronic low dose-rate gamma-ray exposure increased the body weights of mice (figure 2A; $p < 0.01$; C + SE vs. IR + SE and C + EE vs. IR + EE). EE housing reduced the weight gain attributed to radiation exposure at the same level as the nonirradiated controls ($p > 0.05$; C + SE vs. IR + EE). Although additional devices for exercise (e.g., a running wheel) were not installed, mice housed in an EE weighed less than those in an SE after six weeks. The mechanisms for lower body weight are unclear. Although body weight at the time of tumor inoculation may have affected the tumor rejection response, body weight was not correlated with tumor rejection (figure 2B).

Both radiation exposure and EE housing impacted the proportion of cells in the peripheral blood and spleens (figure 3A and B). The proportions of $CD11c^+$, $F4/80^+$, and $CD45R^+$ cells were not significantly affected by radiation (C+SE vs. IR+SE and C+EE vs. IR+EE), unlike in EE housing (C+SE vs. C+EE and IR+SE vs. IR+EE), indicating that changes in the proportion of these cells could not explain the changes in tumor rejection activity (figure 4). Differences in the proportion of $CD335^+$ cells (a marker of NK cells) indicated that EE housing (C+SE vs. IR+EE) ameliorated its decrease due to radiation exposure (C+SE vs. IR+SE). Likewise, EE housing (C+SE vs. IR+SE) ameliorated a decrease in the proportion of $CD335^+$ cells in the spleen, unlike other cells. These changes in the proportions of $CD335^+$ cells may account for the amelioration of the tumor rejection activity (figure 4).

Previous reports have shown that NK cells were involved in the enhancement of antitumor activity by EE housing [14, 18, 23, 24]. A previous report [19] also found that administrations of anti -asialo GM1 antibody to mice reduced tumor rejection activity and neutralized the enhanced tumor rejection activity attributed to EE housing, suggesting that NK cells participate in the rejection of transplanted OV3121 cells in $B6C3F_1$ female mice. Consistent with past reports, the results shown in figure 3A demonstrate that the reduction in activity due to radiation exposure recovers with EE housing.

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These improvements in NK cell activity may also explain the amelioration of the tumor rejection activity (figure 4).

In our previous reports, the tumor rejection activity was decreased by chronic low dose-rate gamma-ray exposure [11, 12] and increased with EE housing [19]. The present study also shows similar results (figure 4), further supporting those of previous reports [11, 12]. Compared with prior results [19], the degree of enhancement of tumor rejection activity in nonirradiated control mice was lower in this experiment (figure 4), which may have been due to differences in the age of the mice used, since the effect of an EE varies with age [25]. These results indicate that the effect of an EE on older mice is lower than that in younger mice. Changes in the proportion of $CD335^+$ cells and cytotoxic activity of NK cells (figure 3) follow trends similar to those of tumor rejection activity (figure 4), indicating that NK cells may be responsible for this tumor rejection activity. Importantly, decreased antitumor activity caused by radiation exposure (IR+SE) was suggested to alleviate the levels similar to that of the nonirradiated control without EE housing (C+SE vs. IR+EE). These results demonstrate that adverse effects, such as cancer [8] and shortened life span [7], after chronic low dose-rate radiation exposures may be mitigated by EE housing, even when initiated after radiation exposure. However, lifestyle factors also play a significant role in the effects of radiation exposure on humans, and the role of rodent (mouse) housing environments on the effects of radiation exposure at a chronic low dose-rate should be studied further.

CONCLUSION

Environmentally enriched housing conditions in mice can alleviate the adverse effects of chronic low dose-rate gamma-ray exposure, which may involve NK cell activity. Therefore, findings from this study suggest a possibility that, after low-dose-rate irradiation, some lifestyle modifications may mitigate the adverse effects of irradiation.

ACKNOWLEDGMENT

We would like to thank Mr. M. Yoneya (Institute for Environmental Sciences) for providing technical assistance on bleeding mice. Dose rate measurements were supported by the CBS Corporation (Tokyo, Japan). This work was performed under a contract with the Aomori Prefectural Government, Japan.

***Conflicts of interest*:** *Declared none.*

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