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X-Ray-Induced Radioresistance Against High-LET Radiations from Accelerated Neon-Ion Beams in Mice

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1. Introduction

Radiation-induced adaptive response (AR) is the phenomenon of priming low-dose radiation-induced resistance to subsequent challenging radiation at higher doses. As investigations on the conditions essential for AR induction and the underlying mechanisms provide important scientific basis for radiation risk estimates and offer significant insight into the novel biological defense mechanisms regarding protection against radiation, study on AR is of great concern for both public health and academic research (United Nations Scientific Committee on the Effects of Atomic Radiation, 1994). Since the *editio princeps* of the AR concept introduced into radiation biology (Olivieri et al., 1984), this phenomenon has been demonstrated both *in vitro* and *in vivo* (Takahashi & Ohnishi, 2009; Mitchel, 2006; Vares et al., 2006). Though studies on the radiation-induced radioresistance in rodents *in vivo* could be retrospected to the later 1940s (Dacquisto, 1959), the first full-dress investigation on AR in mice started about 50 years later by Yonezawa and colleagues (Yonezawa et al., 1990). In a series of comprehensive studies, a variety of experimental condition combinations of the priming and challenging doses, the interval between the irradiations, and the mouse strain were testified and verified (Yonezawa, 2006), laying a cornerstone of *in vivo* model for AR in mice – successful establishment of the mouse models for AR induction by acute low liner energy transfer (LET) X-irradiations at the whole body level using survival from bone marrow death as the main endpoint, which is the so-called "Yonezawa Effect" in Japan (Takahashi & Ohnishi, 2009). The mouse models for AR induction (Yonezawa, 1996) were with great reliability and reproducibility in different laboratories (Nose et al., 2001; Otsuka et al., 2008;). The induced AR could be generally divided into two phenotypes according to the attitude of the priming dose and the interval between the priming and challenging irradiation, involving different mechanisms: AR induced 2 weeks after a priming irradiation at a dose from 0.3 to 0.5 Gy was due to radioresistance occurred in blood forming tissues which was a Trp53 dependent event (Otsuka et al., 2008; Horie et al., 2002), and interaction

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between blood forming tissue and the central nervous system was thought to contribute to AR induced 2 months after a priming dose at 0.05 or 0.1 Gy (Yonezawa, 2000; Misonoh & Yonezawa, 1997).

AR, as one of the most important phenomena in radiation biology, has been studied for nearly three decades, however, almost all the investigations at the whole body level were performed using low LET X- or gamma-irradiations for both priming and challenging doses. With a significant increase in human activities dealing with space missions outside the earth's magnetic field, health-related concerns on exposures to space radiations become a hot topic to be addressed as the space radiation environment consists of energetic protons and heavy ions in galactic cosmic rays and solar particle events. Some important qualitative differences were found between the biological effects produced by the high LET particulate irradiations in space and the low LET photon exposures commonly encountered on earth (Horie et al., 2002). The accelerator-based experimental studies are important to quantify the health risks (Nelson, 2003) and of interest in the use of particle radiotherapy as well as for the exploration of mechanisms especially underlying high LET radiation effects. The present study is a part of the work in a series of investigations aiming to verify the possible existence of low LET irradiation-induced AR against the detrimental effects from the challenging irradiations with high LET heavy-ion irradiations in mammalians at a whole body level and explore its underlying mechanisms.

2. Materials and methods

2.1 Animals

C57BL/6J Jms strain female mice aged 5 weeks old purchased from SLC, Inc. (Japan), were maintained in a conventional animal facility under a 12 h light-12 h dark photoperiod (lights on from 8:00 a.m. to 8:00 p.m.). Animals housed in autoclaved cages with sterilized wood chips, were allowed free access to standard laboratory chow (MB-1, Funabashi Farm Co., Japan) and acidified water *ad libitum*. Animals were acclimatized to the laboratory conditions for 1 week before use. To avoid possible effects from the developmental condition of the animals, any mouse of 6 weeks old with a significantly higher or lower body weight (more or less than the mean $\pm$ 2 SD) was omitted from this study. Based on the preliminary experiment, in which at least 20 mice were used in each experimental group, in the present study at least 30 mice were used in each experimental group and the experiment was repeated twice. All experimental protocols involving mice were reviewed and approved (Experimental Animal Research Plan No. 07-2023) by The Institutional Animal Care and Use Committee of the National Institute of Radiological Sciences (NIRS), and were performed in strict accordance with the NIRS *Guidelines for the Care and Use of Laboratory Animals*.

2.2 Irradiation

X-rays were generated with an X-ray machine (Pantak-320S, Shimadzu, Japan) operated at 200 kVp and 20 mA, using a 0.50 mm Al + 0.50 mm Cu filter. An exposure rate meter (AE-1321M, Applied Engineering Inc, Japan) was used for the dosimetry. The dose rates for delivering the priming and challenging irradiations were about 0.3 Gy/min and 0.7 Gy/min, respectively. For high LET heavy-ion irradiations, the monoenergetic ion beams of neon particles were generated and accelerated by a synchrotron, the Heavy Ion Medical Accelerator in Chiba (HIMAC) at NIRS, Japan. The beam energy was 400 MeV/nucleon,

corresponding to an average LET of 30 keV/micrometer. A challenging dose of 5.5 Gy was delivered at a rate about 1.5 Gy/min. The mice held in acryl containers were exposed to whole-body irradiation at room temperature.

2.3 The mouse model for induction of adaptive response

One set of the conditions essential for AR induction in the mouse model established by Yonezawa *et al* (Yonezawa et al., 1996) was adopted, verified and confirmed under the experimental conditions in our research facilities, and finally applied to the present study. In brief, the efficient priming dose of X-rays was 0.5 Gy. The timing for delivery of the priming dose and challenging dose were on postnatal ages of 6 and 8 weeks of the mice, respectively. The challenging dose of X-rays at 7.5 Gy was used based on the documented work and our previous report (Monobe et al., 2004; Mouthon et al., 1999; Monobe et al., 2003; Wang et al., 2010). The challenging dose of neon-ion irradiations at 5.5 Gy was determined by preliminary trials with the reference from the reported work and our previous study (Monobe et al., 2004; Monobe et al., 2003; Tomizawa et al., 2000; Wang et al., 2010).

2.4 Biological endpoints

The 30-day survival study: The number of deaths that occurred within the 30-day period after delivery of the challenging dose was recorded. Successful induction of AR was defined as the phenomenon that the priming dose induced significantly the suppression of the mortality caused by the challenging dose. The peripheral blood hemogram: The survivors of the 30-day survival study were anesthetized by CO_2 inhalation. The peripheral blood was collected from femoral artery and then the animals were killed by cervical dislocation. The differential blood cell count was done using a blood cell differential automatic analyzer (SYSMEX K4500, Sysmex Corporation, Japan). The data for each experimental group were from at least 6 mice. Micronucleus test: The bone marrow micronucleus test was carried out according to Schmid (Schmid, 2010) with minor modifications (Chaubey et al., 1993). Bone marrow smears prepared from both femurs were processed for the enumeration of micronucleated polychromatic erythrocytes (MNPCE) and micronucleated normochromatic erythrocytes (MNNCE). The slides were coded to avoid any observer bias. The micronuclei were scored using a light microscope at a magnification of 1000x. At least 5000 cells per mouse were counted and the data per experimental point were from at least 5 mice.

2.5 Statistical analysis

Statistical evaluation of the data was done using the c^2 test and Student's *t*-test when appropriate. Statistical significance was assigned to $P < 0.05$.

3. Results

3.1 Verification of the adaptive response model using low LET X-rays in delivery of both the priming and the challenging irradiations

As in our previous study (Wang et al., 2010), the reproducibility of the model for induction of AR in this system was verified and confirmed again by using X-rays as both the priming dose and the challenging dose. The priming dose at 0.5 Gy adopted from Yonezawa *et al*'s work (Yonezawa et al., 1996) and a challenging dose at 7.5 Gy which resulted in about 80% mortality in C57BL/6J Jms female mice when whole body exposed to X-rays at 8 weeks old,

were delivered to the animals on postnatal ages of 6 and 8 weeks, respectively. Results (Fig. 1, drawn from a representative trial) showed that the priming dose significantly improved the survival from 16.7% to 80.0% in the 30-day survival study after the challenging dose, indicating clearly the successful induction of AR under the conditions in our experimental facilities. Serving also as a positive control, the verification work was performed in parallel to the following investigations with heavy neon-ion irradiations.

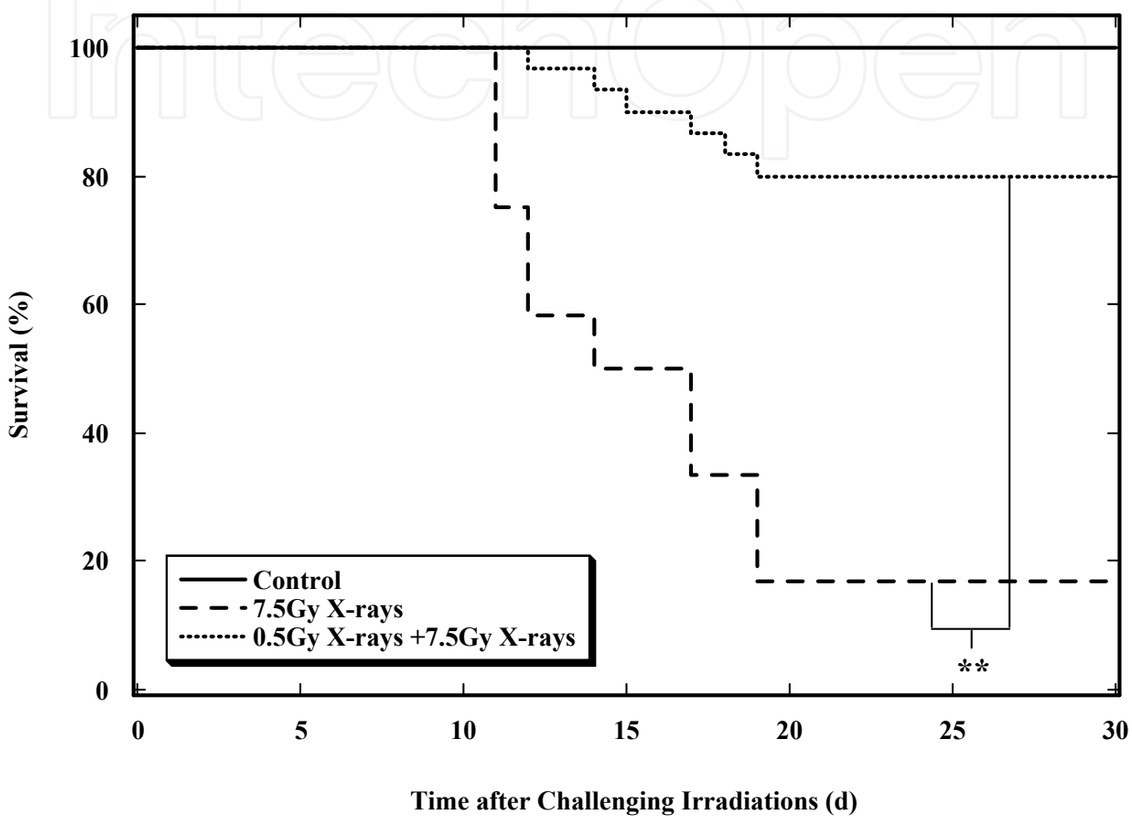


Fig. 1. Thirty-day survival study for the effect from priming low dose of X-rays (0.5 Gy) on the high challenging dose from X-rays (7.5 Gy) in young adult female mice.

The mouse death was recorded after the challenging dose. The solid, broken and dotted lines stand for the "Control" group receiving neither the priming nor the challenging irradiations, the "7.5Gy X-rays" group receiving only the challenging irradiations, and the "0.5Gy X-rays + 7.5Gy X-rays" group receiving both the priming and the challenging irradiations. Two asterisks indicate statistically significant differences at $P < 0.01$ between the two groups compared. This experiment was performed to serve as a positive control, demonstrating that Yonezawa et al's mouse model for induction of AR was successfully reproduced under the conditions in our experimental facilities.

3.2 Effects of the priming dose from low LET X-rays on the killing effect of the challenging dose from high LET heavy neon-ion irradiations

The 30-day survival study was applied to investigate the effects of the priming dose at 0.50 Gy from low LET X-rays on the challenging dose from high LET heavy-ion irradiations with

neon beams in young adult female mice. A representative survival graph obtained using neon ion irradiations as the challenging irradiations at a dose of 5.5 Gy was shown in Figure 2. The priming dose markedly increased the survival rate from 26.1% to 56.7%. These data indicated that a priming dose at 0.50 Gy from low LET X-rays could induce radioresistance against the killing effects from subsequent challenging irradiations with heavy neon-ion beams.

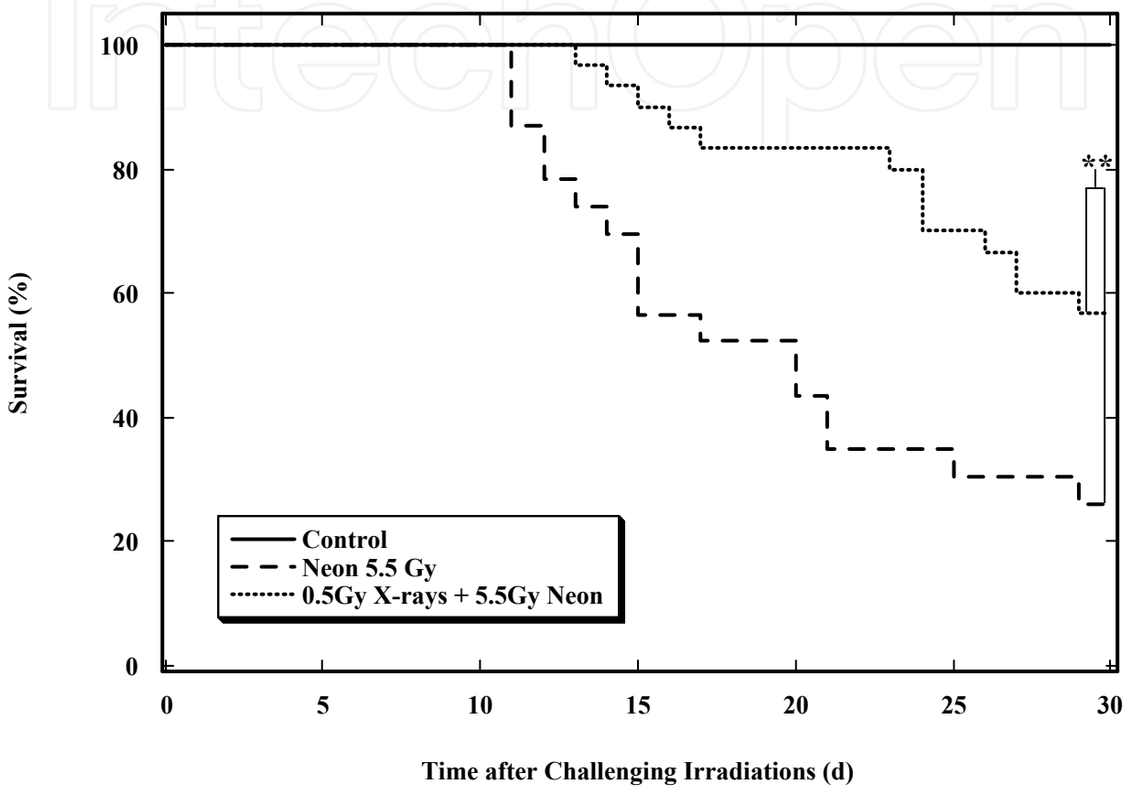


Fig. 2. Thirty-day survival study for the effects from priming low dose of X-rays (0.5 Gy) on the high challenging dose from 5.5 Gy neon-ion irradiations in young adult female mice.

The solid, broken and dotted lines stand for the "Control" group receiving neither the priming nor the challenging irradiations, the "5.5 Gy Neon" experimental group receiving only the challenging irradiations, and the "0.5Gy X-rays + 5.5Gy Neon" experimental group receiving both the priming and the challenging irradiations. Two asterisks indicate statistically significant differences at $P < 0.01$ between the two groups compared.

3.3 Effects of the priming dose from low LET X-rays on the detrimental effect induced by the challenging dose from low LET X-rays or high LET heavy neon-ion irradiations in the hematopoietic system in the survivors

As bone marrow failure was the main cause for the animal death, the residual damage in the hematopoietic system was also studied in the peripheral blood hemogram and the bone marrow cells in the survivors on the following day when the 30-day survival study was finished. Results showed that the priming dose significantly relieved the depression of

peripheral blood platelet counts (Fig. 3). For other blood hemogram indexes, the mean value of leukocyte count in "0.5Gy X-rays + 7.5Gy X-rays" group was slightly higher than that of the "7.5Gy X-rays" group, and no significant effect on improvement of erythrocyte count and leukocyte count was observed (data not shown).

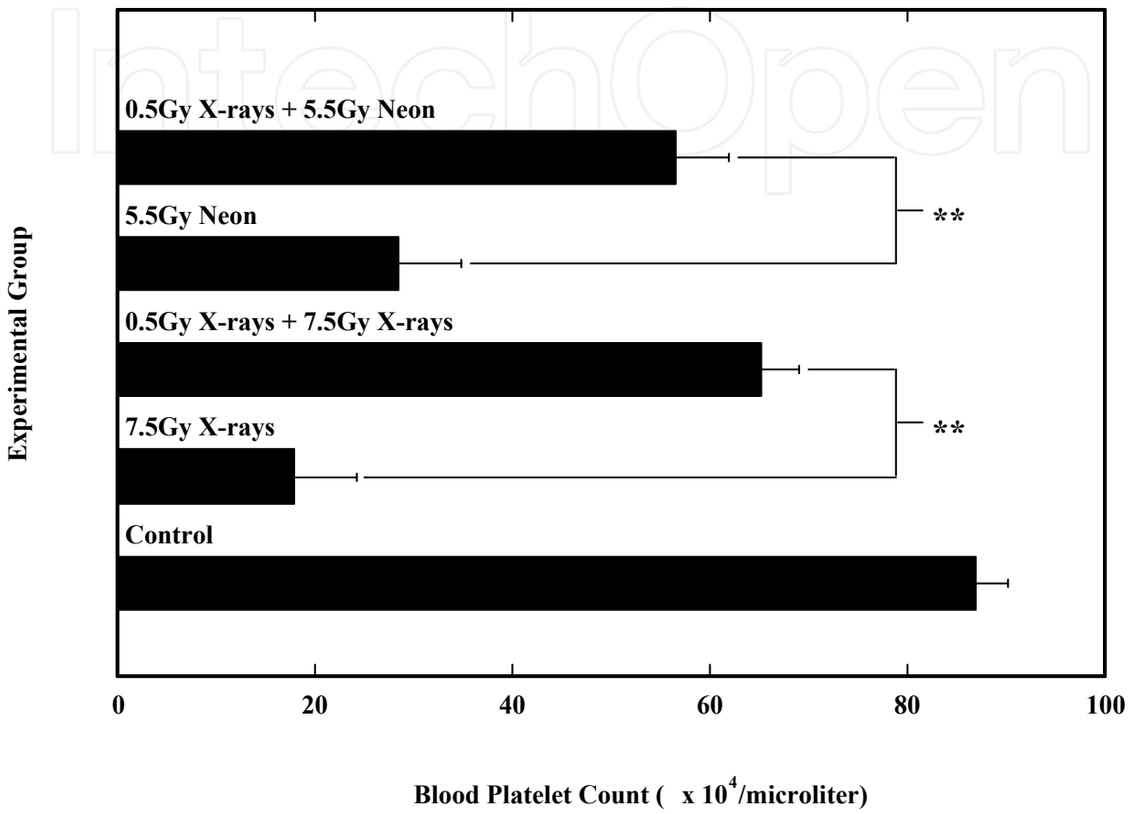
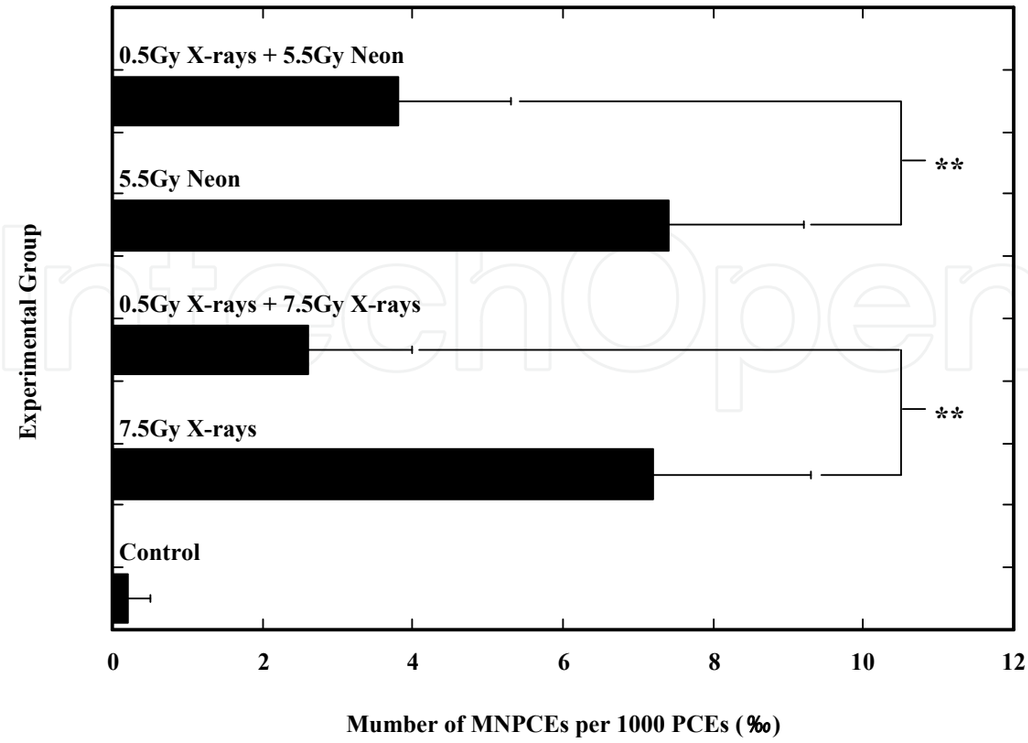


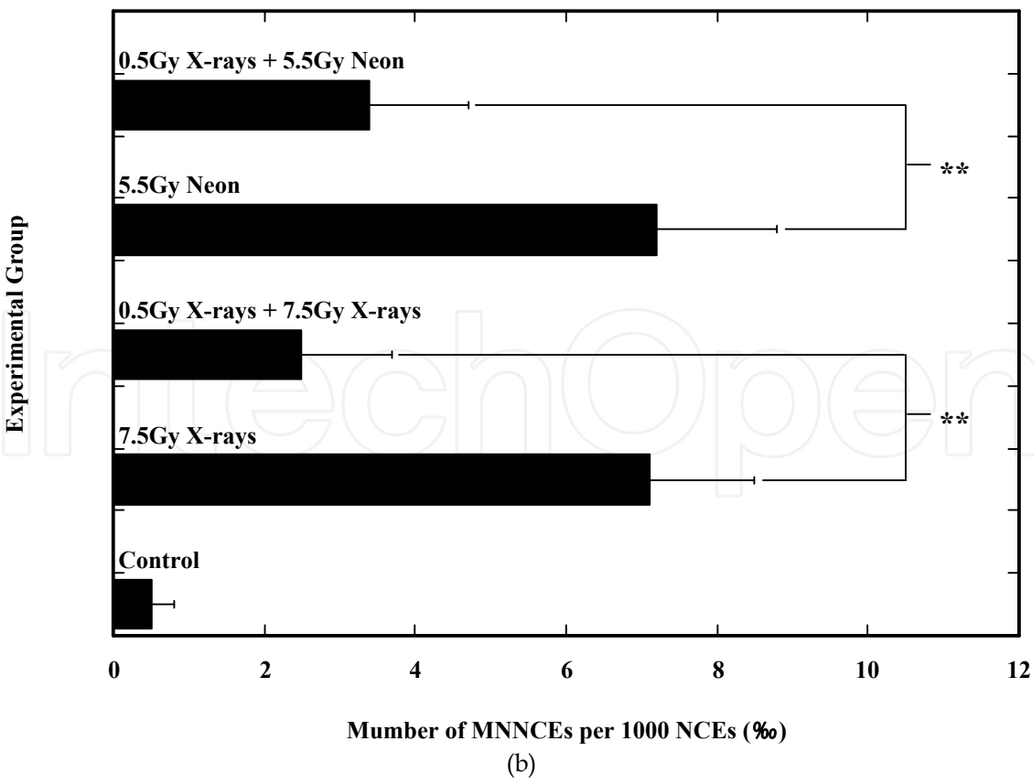
Fig. 3. Peripheral blood hemogram measurement in the survivors on the following day after the 30-day survival study.

Peripheral blood hemogram study in the survivors on the following day when the 30-day survival study was finished for the residual damage in young adult female mice receiving a high challenging dose from X-rays (7.5 Gy) or neon-ion irradiations (5.5 Gy) with or without a priming low dose of X-rays (0.5 Gy). The peripheral blood was collected from femoral artery of the survivors in the 30-day survival study. Two asterisks indicate statistically significant differences at $P < 0.01$ between the two groups compared.

Micronucleus test study showed that the priming dose markedly improved the ratio of polychromatic erythrocytes (PCEs) to the sum of PCEs and normochromatic erythrocytes (NCEs) (data not shown). The priming dose significantly reduced the occurrences of both micronucleated polychromatic erythrocytes (MNPCEs) (Fig. 4A) in PCEs and micronucleated normochromatic erythrocytes (MNNCEs) in NCEs (Fig. 4B). These data indicated that a priming dose at 0.50 Gy from low LET X-rays could induce radioresistance against the detrimental effects from subsequent challenging irradiations with X-rays or neon-ion beams in the hematopoietic system.



(a)



(b)

Fig. 4. Micronucleus test in the survivors on the following day after the 30-day survival study.

Micronucleus test study in the survivors on the following day when the 30-day survival study was finished for the residual damage in young adult female mice receiving a high challenging dose from X-rays (7.5 Gy) or neon-ion irradiations (5.5 Gy) with or without a priming low dose of X-rays (0.5 Gy). The "Control" group receiving neither the priming nor the challenging irradiations, the "7.5Gy X-rays" group receiving only the challenging irradiations, and the "0.5Gy X-rays + 7.5Gy X-rays" group receiving both the priming and the challenging irradiations from X-rays. The "5.5Gy Neon" group receiving only the challenging dose of 5.5 Gy from neon-ion irradiations, and the "0.5Gy X-rays + 5.5Gy Neon" group receiving both the priming of 0.5Gy from X-rays and the challenging dose of 5.5 Gy from neon-ion irradiations. Bone marrow smears were prepared from both femurs of the survivors in the 30-day survival study and processed for the enumeration of micronucleated polychromatic erythrocytes (MNPCE) and micronucleated normochromatic erythrocytes (MNNCE). Two asterisks indicate statistically significant differences at $P < 0.01$ between the two groups compared.

3.4 Effects of the priming dose from low LET X-rays on the reduced body weight gain induced by the challenging dose from low LET X-rays or high LET heavy carbon-ion irradiations in the survivors

The body weight was also scored in survivors in the 30-day survival study. For most of the time points measured, the body weight of either of the irradiated groups was markedly lower than that of the "Control" group after challenging irradiations. Results showed that the priming dose (0.50 Gy of X-rays) significantly suppressed the reduction in the body weight gain two weeks and three weeks, or at three weeks after the challenging dose of 7.5 Gy X-rays or 5.5 Gy of neon-ion irradiations (Fig. 5, Fig. 6). As the death cases were always with a low body weight and the significantly decreased reduction in the body weight was observed in the middle course of the 30-day survival study, the statistical significance was thought not to be of a markedly biological meaning. Of note, the body weight in animals that survived by AR was always significantly lower than the control group at the time from two weeks after the challenging irradiation to the end of the study, indicating the priming dose could rescue the animals from death but it could not completely prevent the damage from the challenging dose to the animals. In addition to the endpoints of the hematopoietic system, body weight is also a sensitive indicator.

The mouse body weight was recorded after the challenging dose. The solid, broken and dotted lines stand for the "Control" group receiving neither the priming nor the challenging irradiations, the "7.5Gy X-rays" group receiving only the challenging irradiations, and the "0.5Gy X-rays + 7.5Gy X-rays" group receiving both the priming and the challenging irradiations. One and two asterisks indicate statistically significant differences at $P < 0.05$ and $P < 0.01$ respectively between the "7.5Gy X-rays" group and the "0.5Gy X-rays + 7.5Gy X-rays" group.

The mouse body weight was recorded after the challenging dose. The solid, broken and dotted lines stand for the "Control" group receiving neither the priming nor the challenging irradiations, the "5.5Gy Neon" group receiving only the challenging irradiations, and the "0.5Gy X-rays + 5.5Gy Neon" group receiving both the priming and the challenging irradiations. One asterisk indicates statistically significant differences at $P < 0.05$ between the "5.5Gy Neon" group and the "0.5Gy X-rays + 5.5Gy Neon" group.

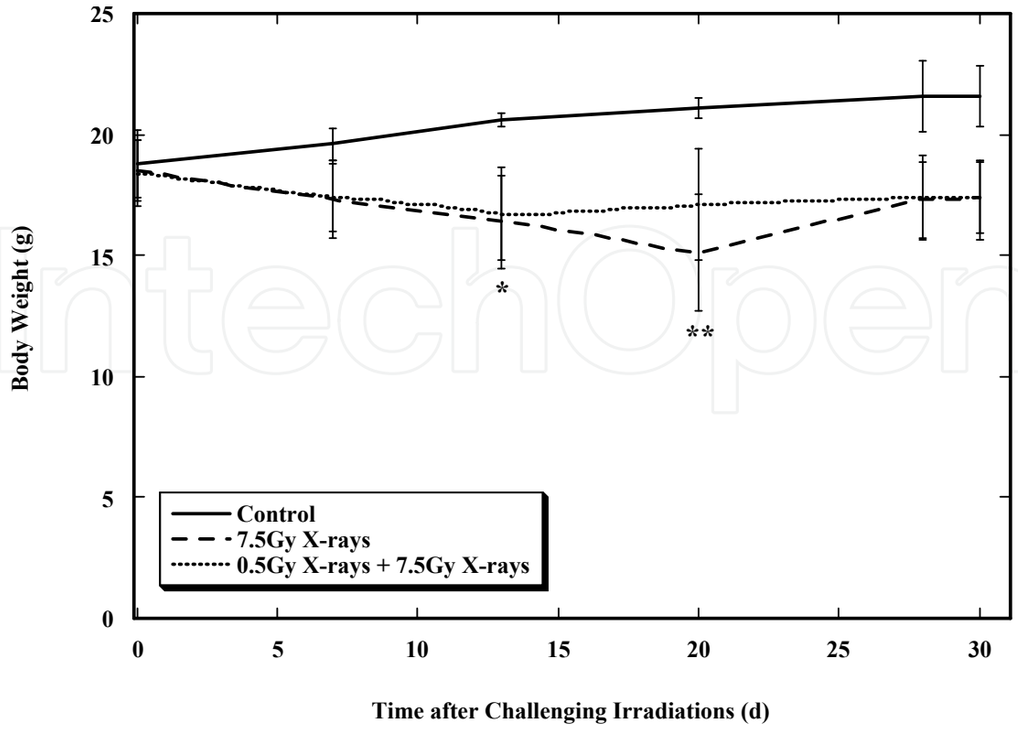


Fig. 5. Body weight study for the effects from priming low dose of X-rays (0.5Gy) on the high challenging dose from X-rays (7.5 Gy) in young adult female mice.

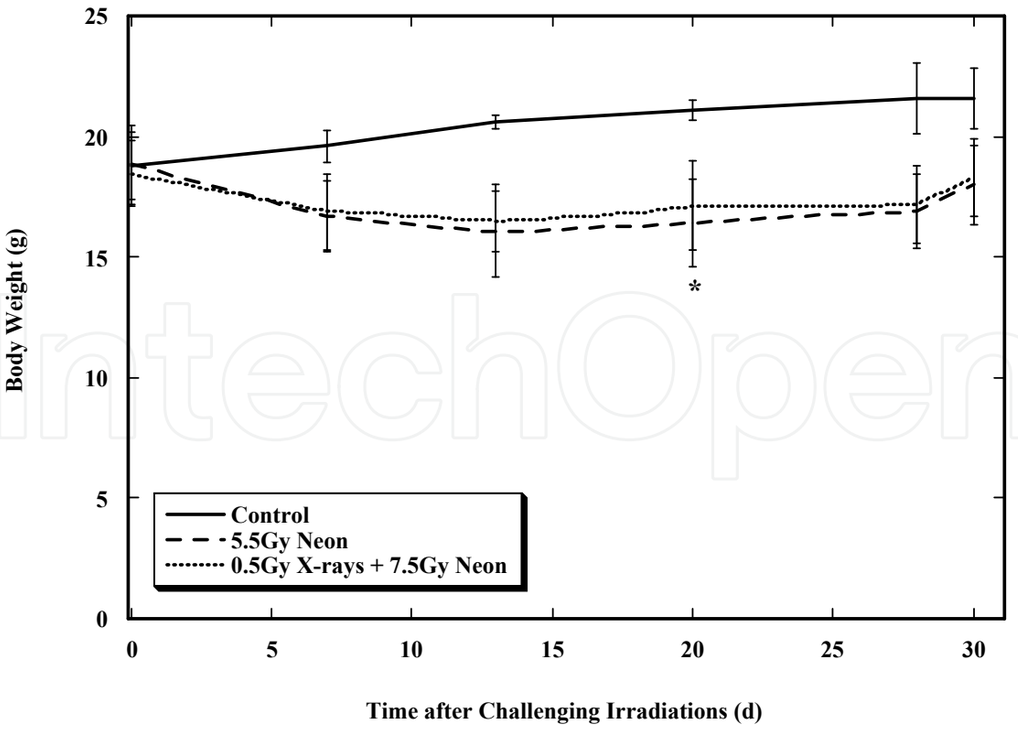


Fig. 6. Body weight study for the effects from priming low dose of X-rays (0.5Gy) on the high challenging dose from neon-ion irradiations (5.5 Gy) in young adult female mice.

4. Discussions

Low doses of low LET irradiations induce protective effects through possible mechanisms such as enhancement of antioxidative capacities, increase in cellular DNA double-strand break repair capacity leading to reduction of initial DNA damage in AR in mice *in vivo* (Otsuka et al., 2006), and reduction of cell death, chromosomal aberrations, mutations, and malignant transformation *in vitro*. These induced responses have been tightly conserved throughout evolution, suggesting that they are basic responses critical to life (Mitchel, 2006). Induction of AR may provide protection of the space mission crews and travelers (Mortazavi et al., 2003), the occupational radiation workers, and the normal tissues and organs of patients receiving heavy-ion radiotherapy. Considering the unavoidable exposure to high LET irradiations during varied human activities, it is crucial and of an on-the-spot inspection to study the possibility of triggering an AR against high LET irradiations in suitable biological models. In our series of investigations using AR model in mice, induction of AR was attempted using X-rays as priming irradiation in combination with challenging irradiations from four kinds of accelerated heavy ions of carbon, neon, silicon and iron with the LET values of about 15, 30, 55, and 200 keV/micrometer respectively. Results showed that a priming low dose of X-rays at 0.5 Gy significantly reduced the mortality from the high challenging dose of carbon, neon or silicon particles, but not iron particles. In addition, the priming low-dose of X-rays also markedly reduced some of the other detrimental effects in the survivors. In the present mouse model for AR induction, the mechanisms responsible for rescue of bone marrow death are mainly of priming irradiation-induced radioresistance to the challenging irradiation-induced Trp-53 derived-apoptosis in hematopoietic stem cells (Horie et al., 2002; Okazaki et al., 2007). Recovery of blood platelet counts after exposure is one of the most important factors for restoration of bone marrow death (Takeda et al., 1981). Results on blood platelet counts obtained in the present study are consistent with this conclusion.

The recovery ratio of the potentially lethal damage depended on the quality of radiations (Suzuki et al., 2000a) and cellular radiosensitivity correlated with the frequency of residual chromatin breaks (Suzuki et al., 2000b). Compared to X-rays, carbon ions induced higher rate of residual chromatin breaks per cell per Gy (Suzuki et al., 1998). Though high LET heavy-ion irradiations generally induces qualitatively different DNA damage such as clustered DNA damage than that of low LET irradiations, for certain cases, such as the results obtained on carbon, neon and silicon ion irradiations in our studies, the X-ray-induced biological defense mechanisms may be as effective countermeasures, being sufficient enough against the damages caused by challenging dose from these high LET irradiations. In fact, *in vitro* study showed that low doses of low LET X-irradiations were effective in reducing chromosomal aberrations induced by high LET irradiations from radon exposure (Wolff et al., 1991). Mechanism studies using cultured human fibroblasts reported that gene expression profiles following gamma-radiation and decays of high-LET-like ^{125}I shared the majority of genes in common, which indicated the involvement of similar pathways in signal transduction after radiation exposures of different modalities (Sokolov et al., 2006a) and DNA DSB may not be the major factor modulating changes in gene expression following irradiation (Sokolov et al., 2006b). These findings suggest that it may share at least to a large extent the same mechanisms against the damages caused by the high dose of challenging irradiations from low LET X-rays or from high LET carbon, neon and

silicon ions. On the other hand, AR was not observable against, even at a small dose (LD5/30), the high LET challenging irradiations from iron ions (Wang et al., 2010). This indicates that the biological defense mechanisms induced by priming low LET X-rays are not, at least not sufficiently enough, capable of dealing with the damage caused by iron-ion irradiations, which seems probably qualitatively different from those induced by carbon, neon, or silicon ion irradiations. There is no a clear conclusion on if the killing effect from heavy ion irradiations at the whole body level is an event depending on either the LET values of the radiation or the ion species, or both. While *in vitro* studies suggested, for the same kind of ion species, heavy ion-induced cell killing effect is of LET dependency (Aoki et al., 2000). Study on the RBE values of carbon ion irradiations relative to X-rays for reproductive cell death showed LET dependent cell killing effects with the RBE values ranging from 1.06 to 1.33 for 13 keV/micrometer and from 2.00 to 3.01 for approximate 77 keV/micrometer irradiation (Suzuki et al., 2000c). For the different ion species, it was also reported that the cell killing effects varied with differences in the energy deposition track structures of the different ion sources, being of LET and ion species dependence: RBE for carbon ions increased steeply up to around 98 keV/micrometer (4.07), while the neon, silicon and iron ions showed maximum peaks around 180 keV/micrometer (3.03 to 3.39) (Tsuruoka et al., 2005). The mutation induction investigations also suggest that different ion species may cause qualitative and quantitative difference even if the LET values are similar (Suzuki et al., 2009; Tsuruoka et al., 2004; Suzuki et al., 2003). It should be noticed that in the cell culture system, though the enhanced clustering of ionization and DNA damage lowered the energy efficiency for producing damage resulting in low RBE values when the LET values of heavy ions exceeded 100 keV/micrometer (Mehnati et al., 2005), the fate for most of the cells hit by the heavy ions is death due to the unrepairable complexity of DNA damage. The biological sequences in vivo after iron-ion irradiations in our previous study should be the case thus AR could be not induced.

Depending on improvement in irradiation facilities, it will be possible to verify if this event depending on either LET or ion species or both when generation of heavy ion irradiations of the same ion species at different LET values and generation of different ion species at the same LET value are possible. To understand what extent low dose irradiations could be beneficially functional in humans, a better understanding of AR and other non-targeted effects other non-targeted effects is needed (Tapio & Jacob, 2007). Radiation quality dependent biological effects must be studied in the context of the mixed high- and low-LET radiations that are found in the space environment. In a recent study, a statistically significant increase in the yield of chromosomal aberrations in lymphocytes from cosmonauts at their first flight long-term space missions was observed. However, for cosmonauts involved in two or more space flights, the yield of aberrations at the end of the last mission was generally in the range of background frequencies measured before the first mission (Durante et al., 2003). This study suggests possible existence of AR induced by space irradiations *in vivo*. Further investigations on AR induction by low dose high LET heavy-ion irradiation and by mixed high- and low-LET radiations are needed. In addition to AR study, radiation effects from high LET irradiations in mammalians on such as development, behavior, mutation and carcinogenesis, are also of great interest to be studied on ground with heavy ions of different energy with suitable accelerators using well-designed animal experiments over extended periods of time (Curtis et al., 2004).

Taken together, in this series of studies, though the essential conditions vary on LET values and ion species, successful induction of AR is demonstrated for the first time using low LET X-rays as the priming dose and high LET heavy-ion irradiations as the challenging dose *in vivo* in the mouse model (Table 1.). The findings suggest that the efficacy of the biological defense mechanisms induced by priming dose of low LET X-rays depends on the quality (either the LET value or the ion particle species of the challenging irradiations, or both) of the challenging irradiations.

Priming Dose	Challenging Dose	Adaptive Response
X-Rays	**Carbon**	○
X-Rays	**Neon**	○
X-Rays	**Silicon**	○
X-Rays	**Iron**	×

Table 1. Induction of adaptive response by low LET X-rays again high LET heavy-ion irradiations.

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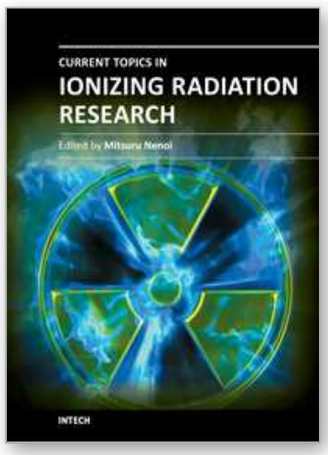
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Since the discovery of X rays by Roentgen in 1895, the ionizing radiation has been extensively utilized in a variety of medical and industrial applications. However people have shortly recognized its harmful aspects through inadvertent uses. Subsequently people experienced nuclear power plant accidents in Chernobyl and Fukushima, which taught us that the risk of ionizing radiation is closely and seriously involved in the modern society. In this circumstance, it becomes increasingly important that more scientists, engineers and students get familiar with ionizing radiation research regardless of the research field they are working. Based on this idea, the book "Current Topics in Ionizing Radiation Research" was designed to overview the recent achievements in ionizing radiation research including biological effects, medical uses and principles of radiation measurement.

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