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## Acquired Radioresistances after Small Doses of X-rays in Mice

Morio YONEZAWA, Jun MISONOH\*, and Yasushi HOSOKAWA

Division of Radiation Biology, Research Center of Radioisotopes,  
Research Institute for Advanced Science and Technology

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### Abstract

Preirradiation with 2.5-15 cGy of X-rays two months before a second exposure to a sublethal dose enhanced the survival rate in mice (ICR strain of Charles River Japan, Co.). Optimal and significant increase was observed with 5-10 cGy. The radioresistance was observed both in male and female mice.

Time study for inducing radioresistance was carried out using male (from the next day till 2 months after preirradiation with 5 cGy) and female (from 2 months till 5 months). The result showed that the radioresistance was observed 2.0-2.5 months after 5 cGy. The resistance did not appear within 1.5 months, and disappeared after 3 months or more.

On the other hand, several authors reported that preirradiation with 50-150 cGy or more resulted in radioresistance about half a month later. We found that preirradiation with 30 or 50 cGy resulted in radioresistance 2 weeks later. This shows that some biological effects may be distinguishable with radiation doses of 5-10 cGy and 30 cGy or more, or that biological effects are quite different with the two dose ranges.

### INTRODUCTION

Recovery from radiation injury has been extensively studied such as in split-dose irradiations. But the overshooting recovery in survival rate after multiple exposures in irradiated animals was scarcely observed. Maisin *et al.* first reported that preirradiation of rats, with as low as 5 cGy of X-rays, increased 30-day survival rate when the animals were again exposed to a sublethal dose about 2.5 months later<sup>1)</sup>. Though the increment was not statistically significant, the study suggested there may be some stimulation after low dose exposure to ionizing radiation. In a previous paper we confirmed that acquired radioresistance was induced in (male) mice 2 months after exposure to 5-10 cGy of X-rays, and that recovery of endogenous CFU-S was stimulated by the preirradiation<sup>2)</sup>.

In the present study, we examined when the radioresistance appears after exposure to 5 cGy of X-rays, and how long it lasts. The result is compared with the acquired radioresistance induced with the priming dose of 30 cGy and more.

\*Present address: Nuclear Engineering Department, Komae Research Laboratory, Central Research Institute of Electric Power Industry, Iwato-kita, Komae, Tokyo 201, Japan

## MATERIALS AND METHODS

### *Animals*

Specific pathogen free 4 week old mice of ICR strain, purchased from Charles River Japan Inc., were kept in a clean-conventional environment. Ten mice were housed in a cage at  $24 \pm 1^\circ\text{C}$  and  $60 \pm 10\%$  relative humidity, and given nutritional chow (NMF of Oriental Yeast Ind. Co. Ltd.) and water *ad libitum*. Acidified water, adjusted to pH 3 by adding HCl into deionized water, was given through automatic valves to the mice to prevent contamination with *Pseudomonas* bacteria. The animals were maintained on a 7 AM-7 PM light-dark cycle, and were acclimated to laboratory conditions for 2 weeks before use.

### *Irradiation*

When 6 weeks old, the animals were whole-body irradiated in a revolving-partitioned-plastic chamber with 5 cGy (or more than 20 cGy, in some cases) of X-rays (260 kV, 15.5 mA, 0.3 mm Cu+0.5 mm Al filter, HVL 0.87 mm Cu, 50 cGy/min). For all experiments, sham-irradiated controls were run concurrently with the preirradiated groups. After a timed interval, the two groups of mice were again exposed to a sublethal dose of 7.0-8.5 Gy.

### *Statistics*

The number of deaths that occurred over the 30-day period was recorded. The difference within the 30-day survival rates of pre-irradiated and sham-irradiated control groups were examined statistically by the Chi-square test applying Yates' correction.

## RESULTS

### *1. Examination of Acquired Radioresistance within 2 Months*

Male mice were irradiated with 7.2-8.5 Gy of X-rays after preirradiation with 5 cGy. Table 1 shows that the 30-day survival rates of the preirradiated group did not exceed

Table 1 Acquired radioresistance within 2 months after 5 cGy of priming exposure in male mice

Interval	Second dose (Gy)	Survival rate		Significance
		5 cGy group	0 cGy group	
1 day	7.2	35.7% (25/70)	28.6% (20/70)	$p > 0.05$
3 weeks	7.75	55.7% (39/70)	62.9% (44/70)	$p > 0.05$
1 month	7.75	62.9% (44/70)	78.6% (55/70)	$p > 0.05$
1.5 months	7.75	62.9% (44/70)	58.0% (40/69)	$p > 0.05$
1.5 months	7.75	56.5% (39/69)	57.1% (40/70)	$p > 0.05$
1.5 months	8.0	24.3% (17/70)	18.3% (11/60)	$p > 0.05$
2 months	7.75	77.2% (44/57)	57.1% (40/70)	$p < 0.05$

significantly those of the sham-irradiated control group when the mice were sublethally exposed 1 day, 3 weeks, 1 month and 1.5 months after the preirradiation.

## 2. *Acquired Radioresistance in Female Mice with 5 cGy of X-rays*

Breeding of male mice (ten per one cage) for more than 2 months after preirradiation sometimes causes fights and injuries. Therefore, female mice were thought to be better for longer experiments. Before starting the longer experiments, acquired radioresistance was examined in female mice. The female mice, at 6 weeks old, were pre-irradiated with 5 cGy, and were irradiated again with 8 Gy 2 months later. Table 2 shows that the priming dose of 5 cGy significantly ( $p < 0.02$ ) enhanced the 30-day survival rate in female mice as well as in males<sup>2)</sup>.

## 3. *Continuity of the Radioresistance*

Female mice were irradiated with 8.0–8.5 Gy 2.5, 3, 4 and 5 months after the preirradiation with 5 cGy. Table 3 shows that the radioresistance continued until 2.5 months after the preliminary exposure, but diminished 3 months later, and did not reappear 4 and 5 months later. The continuity of the acquired radioresistance was observed within 2 to 2.5 months after the priming exposure to 5 cGy.

## 4. *Radioresistance Induced by 30–50 cGy Exposure*

Several authors reported that preirradiation with 50–150 cGy or more resulted in radioresistance about half a month later<sup>3–5)</sup>. Though almost all these reports showed that the mice started to die within 10 days after the second (sublethal) exposure, indicating that the mice might be contaminated with some *Pseudomonas* bacteria, these findings are important and interesting to discuss the low dose effects. We re-examined the effects of the priming dose of 30–50 cGy on the radioresistance of mice. Table 4 shows that preirradiation with 50 cGy enhanced the survival rate after 8 Gy exposure when the mice were irradiated 2 weeks later, but did not 4 weeks later. The priming dose of 30 cGy resulted in a significant radioprotection 2 weeks later, a slight radioprotection 4 weeks later, and no radioprotection 5 weeks later.

Table 2 Acquired radioresistance with 5 cGy of X-irradiation in female mice

Interval	Second dose (Gy)	Survival rate		Significance
		5 cGy group	0 cGy group	
2 months	8.0	90.0% (45/50)	62.9% (44/70)	$p < 0.02$

Table 3 Continuity of the acquired radioresistance after 5 cGy of preirradiation in female mice

Interval	Second dose (Gy)	Survival rate		Significance
		5 cGy group	0 cGy group	
2.5 months	8.5	80.0% (56/70)	59.3% (35/60)	$p < 0.02$
3 months	8.0	86.7% (52/60)	83.8% (57/68)	$p > 0.05$
4 months	8.5	30.0% (21/70)	32.9% (23/70)	$p > 0.05$
5 months	8.5	70.0% (49/70)	61.4% (43/70)	$p > 0.05$

Table 4 Radioresistance induced by 20-50 cGy preirradiation

1st dose (cGy)	Interval (weeks)	2nd dose (Gy)	Survival rate		Significance
			Irrad group	Control	
50	2	8.0	47.5% (19/40)	17.5% (7/40)	p<0.01
50	4	8.0	36.7% (11/30)	40.0% (12/30)	p>0.05
30	2	8.0	80.0% (32/40)	36.0% (18/50)	p<0.001
30	4	8.0	43.3% (26/60)	25.0% (15/60)	p>0.05*
30	5	8.0	65.7% (46/60)	50.0% (35/70)	p>0.05*

\* 0.1 &gt; P &gt; 0.05

## DISCUSSION

Low dose irradiation of mice with 5 cGy induced radioresistance when the mice were sublethally irradiated 2 to 2.5 months later. Nuzhdin noted that a priming dose of 50-250 R induced the increase of radioresistance when mice were again irradiated to 600 R of X-rays two weeks later<sup>4</sup>. Acquired radioresistance, which resulted in mice about half a month after priming irradiation with 50-500 R, was also reported<sup>3,5</sup>. In our present examination, preirradiation with 30 cGy, as well as 50 cGy, resulted in a radioresistance 2 weeks later. There seems to be two types of acquired radioresistances depending on the preirradiation dose: one with 5-10 cGy; appears 2 months later, and the other with 30 cGy or more; appears half a month later. This shows that biological effects are quite different with the two radiation dose ranges. We are now examining whether any radioresistance occurs within the intermediate time interval (2 weeks-2 months) after exposure with the intermediate dose range (20-30 cGy).

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