p53 Dependency of Radio-adaptive Responses in Endogenous Spleen Colonies and Peripheral Blood-cell Counts in C57BL Mice

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p53 knockout mouse / Adaptive response / Blood cell counts / Endogenous spleen colonies / X-irradiation

Radio-adaptive responses at a conditioning X-ray dose of 0.45 Gy and a challenging dose of 5.0 Gy on hematopoietic indices were studied in C57BL mice with p53 (Trp53) wild, heterogenous and knockout allele. The conditioning irradiation, given 2 weeks before the challenging irradiation, induced radio-adaptive responses observed as a recovery of the peripheral blood-cell counts of leukocytes, thrombocytes and erythrocytes on day 14 after challenging irradiation in C57BL mice of the wild-type p53(+/+) . The pre-irradiation also increased the endogenous spleen colonies (endo-CFU-S) on day 12 and the spleen weight on day 14. On the contrary, the knockout p53(−/−) mice gave no such radio-adaptive response. The heterogenous p53(+/−) mice gave an intermediate response. The radio-adaptive response in hematopoiesis at a challenge dose of 5.0 Gy seems to be a p53-dependent phenomenon. The possible role of induction in radio-resistance through the reduction of p53-driven apoptosis in hematopoietic stem cells in pre-irradiated mice is discussed.

INTRODUCTION

The priming exposure of cells to low doses of ionizing radiation induces resistance to a subsequent large dose of radiation. This phenomenon, called radio-adaptive response, has been the focus of considerable interest since its discovery1–3). Numerous in vitro and in vivo adaptive responses have also been reported4–12). We have reported that priming irradiation of 0.3–0.5 Gy two weeks before mid-lethal irradiation induced radio-resistance and decreased the incidence of bone-marrow death in mice5,10). However, the molecular and biological mechanisms of the radio-adaptive response in whole animals have yet to be investigated. On the other hand, p53 has been reported to play an important role in maintaining genomic stability during the cell-cycle checkpoint and as an effector of DNA repair and apoptosis13). Numerous in vitro studies indicate that p53 (or Trp53) is involved in the proliferation, differentiation, and apoptosis of hematopoietic cells14–20).

Because we can not obtain as many as the 60 p53 knockout mice, simultaneously, needed for a survival-rate study, we investigated whether the adaptive response in hematopoiesis, observed as blood-cell counts, the number of endogenous CFU-S and spleen weight after a lower challenging irradiation of 5.0 Gy, depends on p53 or not, by using p53 knockout (−/−), heterogenous (+/−) and wild (+/+ ) type mice of the C57BL strain. Since a challenging dose of 5.0 Gy does not result in the death of the irradiated animals, this study did not elucidate the mechanism of the acquired

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radio-resistance in mouse survival, or a reduction of bone-marrow death, that has been observed at a lethal challenging dose of 6.5 Gy or more\(^1\–^6,12\).

**MATERIALS AND METHODS**

**Animals**

A pair of \(p53\) heterogenous (+/–) mice of the C57BL strain, maintained for 18 generations until then, were kindly provided by Prof. Niwa, Radiation Biology Research Center, Kyoto University. The animals were bred and kept in a clean conventional environment at 24 ± 1°C and 60 ± 10% of relative humidity, maintained in a 7 am to 7 pm light-dark cycle, and given nutritional chow (MNF, Oriental Yeast Co. Ltd.) and water ad libitum. Acidified water, by adjusting the pH to about 2.7 by adding HCl into tap water, was given to the animals to prevent contamination by bacteria.

Primers 1–3 were used simultaneously to detect \(p53\) wild-type (+/+), heterogenous (+/–) and knock-out (−/−) alleles, respectively. Primer 1 (5’): AAT-TGACAAGTTATGCATCCATACAGTACA, specific for the wild-type allele. Primer 2 (3’): ACTCCTCAA-CATCCTGGGGCAGCAACAGAT, common for both mutated and wild-type alleles. Primer 3 (5’): GAAC-CTGCGTGCAATCCATCTTGTTCAATG, present only in the knock-out allele. PCR (TaKaRa PCR Thermal Cycler MP) was performed using about 4 µg of genomic DNA and the products were separated by agarose gel electrophoresis.

The animal experiments were conducted according to the Guideline for Animal Welfare and Experimentation issued by the Research Institute for Advanced Science and Technology, Osaka Prefecture University.

**Irradiation**

When 8–10 weeks old, the animals were pre-irradiated with 0.45 Gy in a revolving, partitioned, plastic chamber with X rays (260 kV, 12.0 mA, 0.3 mm Cu + 0.5 mm Al filter, HVL 0.90 mm Cu, 0.45 Gy/min). A universal dosimeter (RAMTEC 1000) was used for the dosimetry. After an interval of 14 days, pre-irradiated and non pre-irradiated (sham-irradiated) mice were again irradiated with a challenging dose of 5.0 Gy. For all of the experiments, a non pre-irradiated group was run concurrently with a pre-irradiated group.

**Hematological examinations**

Peripheral blood was obtained from the infraorbital venous plexus under anesthesia. The mice were then killed by cervical dislocation. The number of blood cells was automatically counted with a Sysmex K-1000 blood cell counter (Sysmex Inc., Japan). Spleens removed from the mice were weighed and fixed in Bouin’s solution. Colonies on the surface of the organ were counted as endogenous spleen colonies (endo-CFU-S) under a magnifying glass.

**Statistics**

The data were expressed as average ± standard deviation. The difference in the blood-cell counts, numbers of endo-CFU-S and weight of the spleen between the pre-irradiated and non pre-irradiated groups were statistically examined by a Student’s t-test; \(p < 0.05\) was considered to be significant.

**RESULTS**

**Effect of pre-irradiation on the blood-cell counts after a challenging exposure**

Peripheral blood was collected on day 14 after a challenging exposure of 5.0 Gy. At the time it was adequate for estimating the effects of a radio-protective treatment on the recovery of blood-cell counts\(^21\). Fig. 1 shows the blood cell counts of leukocytes (1A), thrombocytes (1B) and erythrocytes (1C). There was no difference in the blood-cell counts of control (without irradiations) animals among the \(p53(+/+)\), (+/–) and (−/−) groups. The blood-cell counts on day 14 after challenging exposure of the non pre-irradiated group were, in descending order, in the \(p53\) (−/−) group > \(p53\) (+/–) group > \(p53\) (+/+) group. In wild

N30001 chamber (Toyo Medic Co., Ltd., Tokyo) was used for the dosimetry. After an interval of 14 days, pre-irradiated and non pre-irradiated (sham-irradiated) mice were again irradiated with a challenging dose of 5.0 Gy. For all of the experiments, a non pre-irradiated group was run concurrently with a pre-irradiated group.
p53(+/-) type animals, the pre-irradiation significantly stimulated the recovery of the blood-cell counts of leukocytes (p < 0.01), thrombocytes (p < 0.001) and erythrocytes (p < 0.001). The effect of pre-irradiation was significant, but less so in the p53(+/-) group than in the p53(+/+) group; p > 0.05 for leucocytes, p < 0.001 for thrombocytes and p < 0.05 for erythrocytes. However, there were no significant effects of pre-irradiation on the blood-cell counts in p53(-/-) mice.

Effect of pre-irradiation on endogenous spleen colonies (endo-CFU-S) after a challenging exposure

Figure 2 shows endo-CFU-S on days 10, 11 and 12 after a challenging exposure to 5.0 Gy. In the non pre-irradiated group of p53(+/+) animals, the spleen colonies gradually increased among the observed period of days 10–12, and the pre-irradiation significantly increased the colony count on day 12. In p53(+-) animals, the increase in the number of the colonies was
much faster than the wild-type, but the pre-irradiation did not have any significant effects on endo-CFU-S, though the number of pre-irradiated group was comparatively higher than that of the non pre-irradiated group on days 10–12. On the other hand, a large number (more than 50) of endogenous CFU-S was formed on day 8 after 5.0 Gy in $p53^{(-/-)}$ animals of both the pre-irradiated and non pre-irradiated groups. A great number of colonies fused, and we could not count the number on day 10.

**Effect of pre-irradiation on the spleen weight after a challenging exposure**

Figure 3 shows the spleen weight after challenging irradiation of 5.0 Gy. A decrease in the spleen weight was observed even 6 hr after challenging irradiation with 5.0 Gy in $p53^{(+/-)}$ mice. The decrease was similarly significant on the next day in the weight of both the pre-irradiated and non pre-irradiated groups. However, no loss in the spleen weight was observed in $p53^{(-/-)}$ mice throughout the observation time up to day 14. The loss of spleen weight in the $p53^{(+/-)}$ group was significant, but showed intermediate values between the two ($p53^{(+/+)}$ and $p53^{(-/-)}$) groups 6 hr, 1 day and 10 days after challenging irradiation. There were no effects of pre-irradiation on the spleen weight until day 10 after challenging irradiation in all three $p53^{(+/+)}$, $p53^{(+/-)}$ and $p53^{(-/-)}$ groups. The recovery of the spleen weight was much faster in the $p53^{(+/-)}$ group than in the $p53^{(+/+)}$ group. The spleen weight in $p53^{(+/-)}$ mice of both the pre-irradiated and non pre-irradiated groups similarly recovered on day 14, showing that there were no effects of pre-irradiation on the recovery of the spleen weight in $p53^{(+/-)}$ mice. A significant effect of pre-irradiation on the recovery of the spleen weight was only observed in the wild-type $p53^{(+/+)}$ animals on day 14.

**DISCUSSION**

Previously, we reported on the radio-adaptive survival response in mice, induced 14 days after priming irradiation with 0.3–0.5 Gy of X rays, and suggested that the adaptive response within blood-forming tissues might be concerned with that phenomenon\(^7\). In the present study we examined the effects of priming exposure of 0.45 Gy given 14 days before challenging
irradiation with non-lethal 5.0 Gy on the following hematopoietic indices in C57BL/6 mice: the spleen weight, endogenous-CFU-S and peripheral blood cell counts. We also examined whether the adaptive response in hematopoiesis depends on p53 or not, since p53 has an important role as an effector of DNA repair and apoptosis13). As reported by Nose et al.12), after lethal dose irradiation, the depletion of radiation-induced peripheral blood-cell progressed beyond day 15, and reached the nadir at day 20 without any recovery. We also reported that the peripheral blood-cell counts on day 14 and 15 after a non-lethal 5.5 Gy were not influenced by pre-irradiation in mice of the ICR strain6). Therefore, the adaptive responses in the three indices observed in the present study did not directly account for the mechanism of the radio-adaptive survival response, since no mice died from bone-marrow death at 5.0 Gy, applied in the present study.

Peripheral leukocytes, thrombocytes and erythrocytes on day 14 after challenging irradiation of 5.0 Gy, at an adequate time for estimating the recovery of the blood-cell counts21), were compared within the pre-irradiated and non pre-irradiated groups. The effects of pre-irradiation were significant in the p53(+/+) group. Nevertheless, the increment of blood-cell counts by pre-irradiation was very small compared with that induced by some radioprotective substances25–29). There were absolutely no effects of pre-irradiation on the three blood-cell counts in the p53(−−) group. Mice in the p53(+/−) group showed intermediate effects of pre-irradiation.

Endogenous CFU-S counts are interpreted as evidence of the expansion of the stem-cell pool23). The number of endo-CFU-S in the p53(+/−) group of mice was more than 50 on day 8 after challenging irradiation, independently of the priming exposure. Endogenous spleen colonies on days 10 to 12 after challenging exposure of 5.0 Gy increased with time in the p53(+/−) and p53(+/+) groups. The colony counts of the pre-irradiated group were rather higher than that of the non pre-irradiated group. Significant effects of the pre-irradiation were observed only in the p53(+/+) group on day 12.

We also observed the spleen weight, since the spleen is an important blood-forming tissue in mice. Splenocytes have been reported to undergo p53-dependent apoptosis shortly after whole-body irradiation with a few grays22,23). Radiation-induced Bax and apoptosis detected 12 hr after exposure to 3.0 Gy in the spleens of C57BL/6N mice were reported to be dose-dependent up to 4.5 Gy24). A time of 6 hr after exposure to 5.0 Gy was reported at the maximal point of apoptosis in the spleen25). The spleen weight decreased as soon as 6 hr after challenging exposure in p53(+/+) mice, but was not observed in p53(−−) mice. The p53(+/−) group showed intermediate effects of challenging irradiation. These results might indicate that a loss of the splenocytes by apoptotic death accompanied with elimination by phagocytosis in the spleen was not developed, or only slightly so, after exposure to 5.0 Gy in p53(−−) mice. Pre-irradiation had no effect on the spleen weight 6 hr, 1 and 10 days after challenging exposure in all of the p53(+/+), p53(+/−) and p53(−−) mice. The low value of the spleen weights in the p53(+/+) and p53(−−) groups continued until day 10 after exposure to 5.0 Gy. This might show that pre-irradiation had no effect on preventing a decrease in the spleen weight, or possibly on preventing apoptosis of the majority of splenocytes. Takahashi11) showed that chronic irradiation at a low dose-rate interfered with the p53-centered signal transduction pathway induced by radiation in human cultured cells and C57BL/6 mouse spleen cells, and also showed a significant suppression of p53, Bax and the induction of apoptosis 12 hr after challenge irradiation at 3 Gy. Apoptosis after challenging irradiation in the spleen cells was decreased by priming chronic irradiation from 18% to 2%. Our data seems to be contradictory to that of Takahashi’s, since there were no effects of pre-irradiation on the decrease in the spleen weight. However, this divergence will be explained based on the assumption that if the dose-response curve for the splenocytes was sigmoidal (this is supported by the fact that there is no increase in apoptotic cells in the spleen at 0.50 Gy37), the rate and the number of rescued cells by the pre-irradiation under a similar dose-reduction factors (DRF) might be much smaller at 5.0 Gy than at 3.0 Gy. The pre-irradiation...
might induce radioresistance in hematopoietic stem cells at the radio-resistant G_0 stage in the spleen and bone marrow, and concomitantly stimulated proliferation of the pluripotent hematopoietic stem cells, as suggested by the stimulated recovery of the endo-CFU-S on day 12 as well as the spleen weight on day 14 after challenging exposure to 5.0 Gy in p53(+/-) mice.

There was practically no loss of spleen weight, and no significant increase in the weight during the observation time after challenging exposure in the p53(–/–) mice. The loss of the spleen weight after challenging exposure to 5.0 Gy was smaller in the p53(+/-) group than in the p53(+/-) group, presumably because the number of surviving spleen cells, or without apoptotic death, after the challenging irradiation was more in the p53(+/-) animals than in the wild type p53(+/-) ones.

The involvement of p53-dependent apoptosis in radiation teratogenesis and in the radio-adaptive response in the late organogenesis of mice was reported^{32}. In this case the radiation-induced teratogenesis of digital defects was prevented by pre-irradiation with either 0.05 Gy or 0.30 Gy on embryonic day 11 prior to a challenging irradiation at 3 Gy on embryonic day 12. The p53(+/-) embryos did not show any radio-adaptive response, indicating the involvement of p53 in the radio-adaptive response in embryogenesis.

Sasaki et al.^{33} studied the X-ray-induced adaptive response in cultured mouse and human cells with different genetic background relevant to the DNA damage response pathway, and showed that p53 protein plays a key role in the adaptive response, while the DNA-PKcs, ATM and FANCA genes were not responsible. They concluded that the p53 has a pivotal role in channeling the radiation-induced DNA double-strand breaks into an adaptive legitimate repair pathway, where the signals are integrated into p53 by a circuitous protein kinase C (PKC)-p38 mitogen activated protein kinase (p38MAPK)-phospholipase C (PLC) damage sensing pathway, and hence turning off the signals to an alternative pathway to illegitimate repair and apoptosis. In our present whole-body-study, both the priming dose (0.45 Gy instead of 0.02 Gy) and the interval time (14 days instead of up to 1 day) were different to those in cultured cells. However, the induction of radioresistance through the reduction of p53-centred apoptosis seems to be the same. The induction of the radio-adaptive response observed in vivo in the survival rate and the hematopoietic indices in mice needed much more time than in vitro cell systems. In vivo, it might proceed through several time-consuming steps, such as triggered by T-cell apoptosis, which occurs after the irradiation of 0.5 Gy^{31}.

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REFERENCES

1. Wolff, S. (1996) Aspects of the adaptive response to very low doses of radiation and other agents. Mutat. Res. 358: 135–142.
2. Wolff, S. (1998) The adaptive response in radiobiology: evolving insights and implications. Environ. Health Perspect. 106 Suppl. 1: 277–283.
3. United Nations Scientific Committee on the Effects of Atomic Radiation (1994) Sources and Effects of Ionizing Radiation, Annex B, Adaptive responses to radiation in cells and organisms. United Nations, New York.
4. Yonezawa, M., Takeda, A. and Misonoh, J. (1990) Acquired radioresistance after low dose X-irradiation in mice. J. Radiat. Res. 31: 256–262.
5. Yonezawa, M., Misonoh, J. and Hosokawa, Y. (1996) Two types of X-ray-induced radioresistance in mice: Presence of 4 dose ranges with distinct biological effects. Mutat. Res. 358: 237–243.
6. Yonezawa, M., Misonoh, J., Hosokawa Y. and Asano, T. (1999) Decreased bone marrow death and suppression of hemorrhage in radio-adaptive response in mice. Hoken Butsuri 34: 375-380. [in Japanese]
7. Wang, B., Ohyama, H., Nose, T., Itsukaichi, H., Nakajima, T., Yukawa, O., Odaka, T., Tanaka, K., Kojima E.
and Hayata, I. (1998) Adaptive response in embryogenesis: I. Dose and timing of radiation for reduction of prenatal death and congenital malformation during the late period of organogenesis. Radiat. Res. 150: 120–122.

8. Wang, B., Ohyama, H., Haginoya, K., Odaka, T., Itsukai-
ichi, H., Nose, M., Nakajima, T., Yukawa, O., Yamada, T.
and Hayata, I. (1999) Adaptive response in embryogenesis: II. Retardation of postnatal development of prenatally irradiated mice. Radiat. Res. 152: 119–123.

9. Wang, B., Ohyama, H., Haginoya, K., Odaka, T., Itsukai-
ichi, H., Yukawa, O., Yamada, T., and Hayata, I. (2000) Adaptive response in embryogenesis: III. Relationship to radiation-induced apoptosis and p53 gene status. Radiat. Res. 154: 277–282.

10. Yonezawa, M. (2000) Radioadaptive survival response in mice. In Biological Effects of Low Dose Radiation (C.S. Potten, T. Yamada, C. Mothersill and B.D. Michael, Eds.), pp.93-99. Elsevier Science, Amsterdam.

11. Takahashi, A. (2002) Pre-irradiation at a low dose-rate blunted p53 response. J. Radiat. Res. 43: 1–9. (Special Award Review Article)

12. Nose, M., Wang, B., Itsukaichi, H., Yukawa, O., Hayata,
I., Yamada, T. and Ohyama, H. (2001) Rescue of lethally irradiated mice from hematopoietic death by pre-irradiation to 0.5 Gy X rays without recovery from peripheral blood cell depletion and its modification by OK432. Radiat. Res. 156: 195–204.

13. Lane, D. (1992) p53, guardian of the genome. Nature, 358: 15–16.

14. Donehower, L. A, Harvey, M, Slagle, B. L., McArthur,
M. J., Montgomery Jr., C.A., Butel, J. S. and Bradley, A (1992) Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. Nature 356: 215–221.

15. Kastan, M. B., Radin, A. I., Kuerbitz, S. J., Onyekwere,
O., Wolkow, C. A., Civin, C. I., Stone, K. D., Woo, T.,
Ravindranath, Y. and Craig, R. W (1991) Levels of p53 protein increase with maturation in human hematopoietic cells. Cancer Res. 51: 4279–4286.

16. Schalusky, G., Goldfinger, N., Peled, A., Rotter, V. (1991) Involvement of wild-type p53 in pre-B-cell differentiation in vitro. Proc. Natl. Acad. Sci. USA 88: 8982–8986.

17. Shouman, Y., Dolnikov, A., Mac Kenzie, K.L., Miller, M.,
Chan, Y.Y. and Symonds, G. (1996) Retroviral transduction of hematopoietic progenitor cells with mutant p53 promotes survival and proliferation, modifies differentiation potential and inhibits apoptosis. Leukemia 10: 1619–1628.

18. Lotem, J. and Sachs, L. (1993) Hematopoietic cells from mice deficient in wild-type p53 are more resistant to induction of apoptosis by some agents. Blood 82: 1092-1096.

19. Banerjee, D., Lenz, H. J., Schnieders, B., Manno, D. J.,
Ju, J. F., Spears, C. P., Hochhauser, D., Danenberg, K.,
Danenberg, P. and Bertino, J. R. (1995) Transfection of wild-type but not mutant p53 induces early monocyctic differentiation in HL60 cells and increases their sensitivity to stress. Cell Growth Diff. 6: 1405–1413.

20. Jiang, D., Lenardo, M. J. and Zuniga-Pflucker, C. (1996) p53 prevents maturation to the CD4+CD8+ stage of thymocyte differentiation in the absence of T cell receptor rearrangement. J. Exp. Med. 183: 1923–1928.

21. Yonezawa, M., Katoh, N. and Takeda, A. (1987) A convenient method for the determination of radioprotective activity in substances administered after ionizing irradiation. Radiat. Biol. Res. Comm. 22: 173–175. [in Japanese]

22. Fujikawa, K., Hasegawa, Y., Matsuzawa, S., Fukunaga,
A., Itoh, T. and Kondo, S. (2000) Dose and dose-rate effects of X rays and fission neutrons on lymphocyte apoptosis in p53(+/+) and p53(−/−) mice. J. Radiat. Res. 41: 113–127.

23. Midgley, C. A., Owens, B., Briscoe, C. V., Thomas, D. B. and Lane, D. P. (1995) Coupling between gamma irradiation, p53 induction and the apoptotic response depends upon cell type in vivo. J. Cell Sci. 108: 1843–1848.

24. Takahashi, A., Ohnishi, K., Asakawa, I., Kondo, N., Nakagawa, H., Yonezawa, M., Tachibana, A., Matsumoto, H. and Ohnishi, T. (2001) Radiation response of apoptosis in C57BL/6N mouse spleen after whole-body irradiation. Int. J. Radiat. Biol. 77: 939–945.

25. Takeda, A., Yonezawa, M. and Katoh, N. (1981) Restoration of radiation injury by ginseng. I. Responses of X irradiated mice to ginseng extract. J. Radiat. Res. 22: 323–335.

26. Takeda, A., Katoh, N. and Yonezawa, M. (1982) Restoration of radiation injury by ginseng. III. Radioprotective effect of thermostable fraction of ginseng extract on mice, rats and guinea pigs. J. Radiat. Res. 23: 150–156.

27. Yonezawa, M., Katoh, N. and Takeda, A. (1985) Radiation protection by Acanthopanax senticosus (Rupr. et Maxim.) Harms in mice. Shoyakugaku Zasshi 39: 139–142.

28. Yonezawa, M., Katoh, N. and Takeda, A. (1989) Radiation protection by Shigoka extract on split-dose radiation in mice. J. Radiat. Res. 30: 247–254.

29. Yonezawa, M. (1993) Radioprotective activity in some medicinal herbs. Shoyakugaku Zasshi 47: 338–341.

30. Takahashi, A. (2002) Pre-irradiation at a low dose-rate blunted p53 response. J. Radiat. Res. 43: 1–9.

31. Matsubara, J., Turcanu, V., Poindron, P. and Ina, Y.
(2000) Immune effects of low-dose radiation: Short-term induction of thymocyte apoptosis and long-term augmentation of T-cell-dependent immune responses. Radiat. Res. 153: 332–338.

32. Wang, B. (2001) Involvement of p53-dependent apoptosis in radiation teratogenesis and in the radioadaptive response in the late organogenesis of mice. J. Radiat. Res. 42: 1–10.

33. Sasaki, M.S., Ejima, Y., Tachibana, A., Yamada, T., Ishizaki, K., Shimizu, T. and Nomura, T. (2002) DNA damage response pathway in radioadaptive response. Mutat. Res. 504: 101–118.

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