Acquisition of Radioresistance in Mice Induced by Low Dose-rate Long Term Gamma Irradiation
− Enhancement of Hematopoiesis and Reduction of DNA Damage −

Background

Low dose pre-irradiation would improve the survival of mice after acute high dose irradiation. The acquisition of radioresistance by low dose irradiation is called "radiation adaptive (or radioadaptive) response", which emerged as a specific responses in animals when treated with low dose radiation. However, it is almost observed when the mice were primed with "single low dose" radiation. Therefore, it is necessary to clarify whether the adaptive response is induced and what its mechanism is under "low dose-rate long term" irradiation.

Objectives

To confirm the induction of adaptive response by low dose-rate long term irradiation, we focused on the hematopoietic system, which is most sensitive organ to radiation in mammalian body; survival rate of hematopoietic stem cells (HSCs) *1 after high dose irradiation, reduction of DNA damage and enhancement of antioxidants were estimated as an indicator of radiation resistance.

Principal Results

1. Mice were irradiated with gamma rays at 1.2mGy/hr for 30, 50, 60, 70 and 80 days. Immediately after the irradiation, high dose X-irradiation was carried out. Twelve days later, the number of colonies appearing on the surface of spleen, comprised to HSCs, was counted. The survival of HSCs was increased at 30 or 60 days (Fig.1). It was indicated that low dose-rate long term irradiation could induce adaptive response but it had a specific response.
2. Mice were irradiated at the low dose-rate for 30 days; then they were acutely irradiated with 0.5, 1 or 2 Gy of X-rays. Immediately after the X-irradiation the spleen was removed and DNA damage in spleen cells consisting of HSCs was analyzed. The DNA damage was less in the mice pre-irradiated and then X-irradiated compared to that in the mice irradiated with the X-rays only (Fig.2).
3. One of the antioxidants which can reduce reactive oxygen species was enhanced by low dose-rate irradiation (Fig.3). Reactive oxygen species were known to DNA damaging agents. It is possible to contribute that the reduction of DNA damage by antioxidants finally improves the survival of HSC.

The results described above indicated that the low dose-rate long term irradiation activated certain types of bio-defense mechanisms including an enhancement of antioxidants, reduction of DNA damage and improved HSC survival to prevent the death of heavily irradiated mice.

Future Developments

Identify the molecules or genes that contribute to radiation adaptive response and confirm they are enhanced in humans in the same manner.

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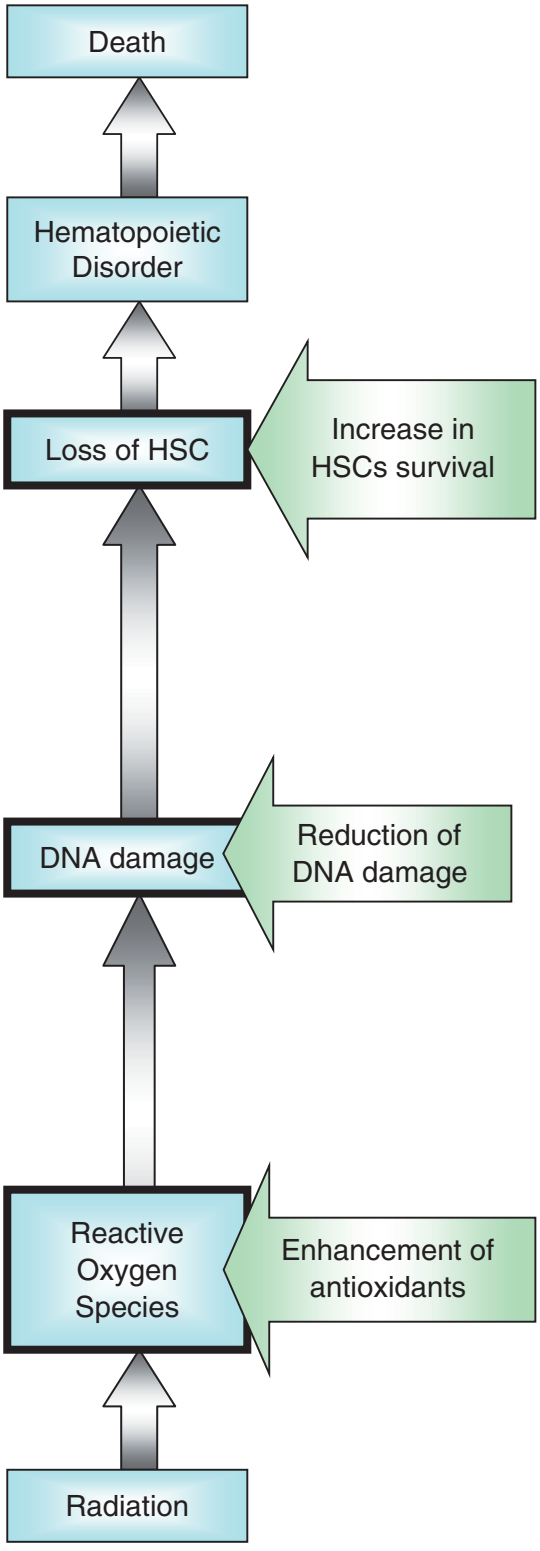
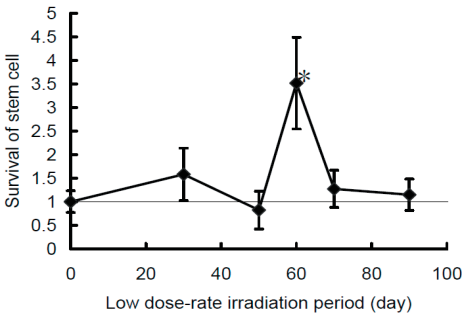
Reference

K. Otsuka, et.al., 2004, "Detection of DNA damage in mouse tissue cells induced by low dose or low dose-rate irradiation", Technical Report G03012 (in Japanese)
K. Otsuka, et.al., 2005, "Radiation adaptive response induced by prolonged low dose-rate irradiation", Technical Report L04003 (in Japanese)

*1 : Primordial cells which produce blood cells such as erythrocyte, leukocyte, lymphocyte and so on. Disorder of hematopoietic system by the loss of HSCs may cause death.





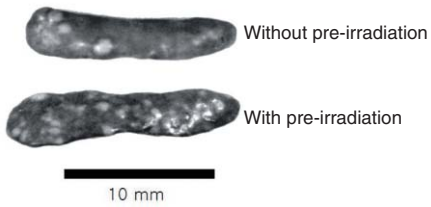


Fig.1 Effects of low dose-rate irradiation on the survival of HSCs

(above) The number of HSCs was specifically increased at 60 days irradiation.

(below) Appearance of the spleen of mice irradiated 60 days at 1.2 mGy/hr. Each colony (seemed as a white nodule) derived from one stem cell.

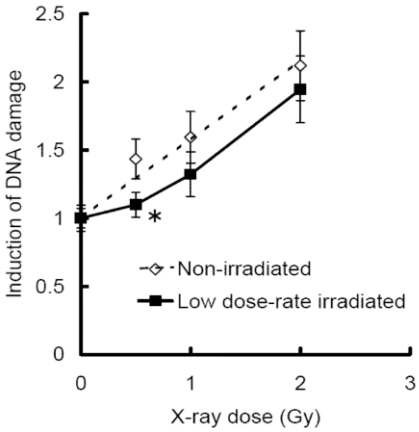


Fig.2 Reduction of DNA damage by low dose-rate irradiation

DNA damage was increased by increasing the X-ray dose. However, relative damage was suppressed in the pre-irradiated mice.

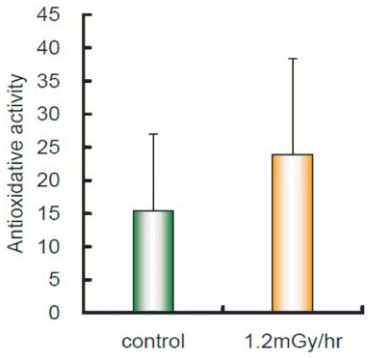


Fig.3 Enhancement of antioxidative activity by low dose-rate irradiation

Low dose-rate irradiation (0.6Gy at 1.2mGy/hr) could induced antioxidative activity in mouse.

【Steps in radiation-induced disorder on hematopoietic system and their prevention by bio-defense mechanisms enhanced by low dose-rate-irradiation】

Certain adaptive responses (shown by green arrows) suppress each radiation inductive disorder (blue).