Effects of Low Dose-rate Radiation Exposure on Hematopoietic-stem-cell Microenvironments and Roles in Regulations of Hematopoietic-stem-cell Behaviors

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Abstract

Chronic radiation exposure at a low dose-rate (LDR) of 20 mGy/day suppresses proliferation of murine hematopoietic stem cells (HSCs). Recent studies have reported that HSC behaviors involving proliferation are dependent on surrounding conditions, called the HSC "niche". Our gene expression analysis of HSCs in LDR-irradiated mice has predicted that the proliferative suppression is caused by extracellular factors. The extracellular factors in the HSC niche have been well investigated and reported to maintain HSC homeostasis, and irregular secretions of them could promote HSC mutation resulting in transformation into leukemic stem cells. Meanwhile, little is known about radiation-induced changes of the HSC niche and effects of these changes on HSCs. In order to clarify the direct and indirect effects of LDR radiation on HSCs, we have analyzed the changes in the HSC niche irradiated *in vivo* and in the niche-free HSCs irradiated *ex vivo*. Here we report the results of the latter analysis, showing the proliferation and differentiation of HSCs after *ex vivo* irradiation. HSCs were isolated from C3H males aged 100 to 150 days and cultured *ex vivo*. The *ex vivo* HSCs were irradiated with 20 mGy/day (LDR), 287 mGy/day (MDR) or 839 mGy/min (HDR) of gamma-rays, and cultured under the non-irradiated condition thereafter. Irradiation at all three dose rates induced proliferative suppression. LDR irradiation to a total dose of 0.4 Gy suppressed cell proliferation completely, whereas a total dose of 1.72 Gy of MDR or HDR irradiation was necessary to induce similar effects. Thus, LDR irradiation seems more effective. In addition, LDR radiation promoted differentiations into $CD8a^{+}CD8b^{+}$ cells. These results, together with the results of our previous *in vivo* whole-body LDR irradiation experiments that the suppression of HSC proliferation was not induced by irradiation with a total dose less than 2 Gy, suggest that *ex vivo* HSCs without their niche might be more sensitive to LDR radiation than their *in vivo* counterparts.

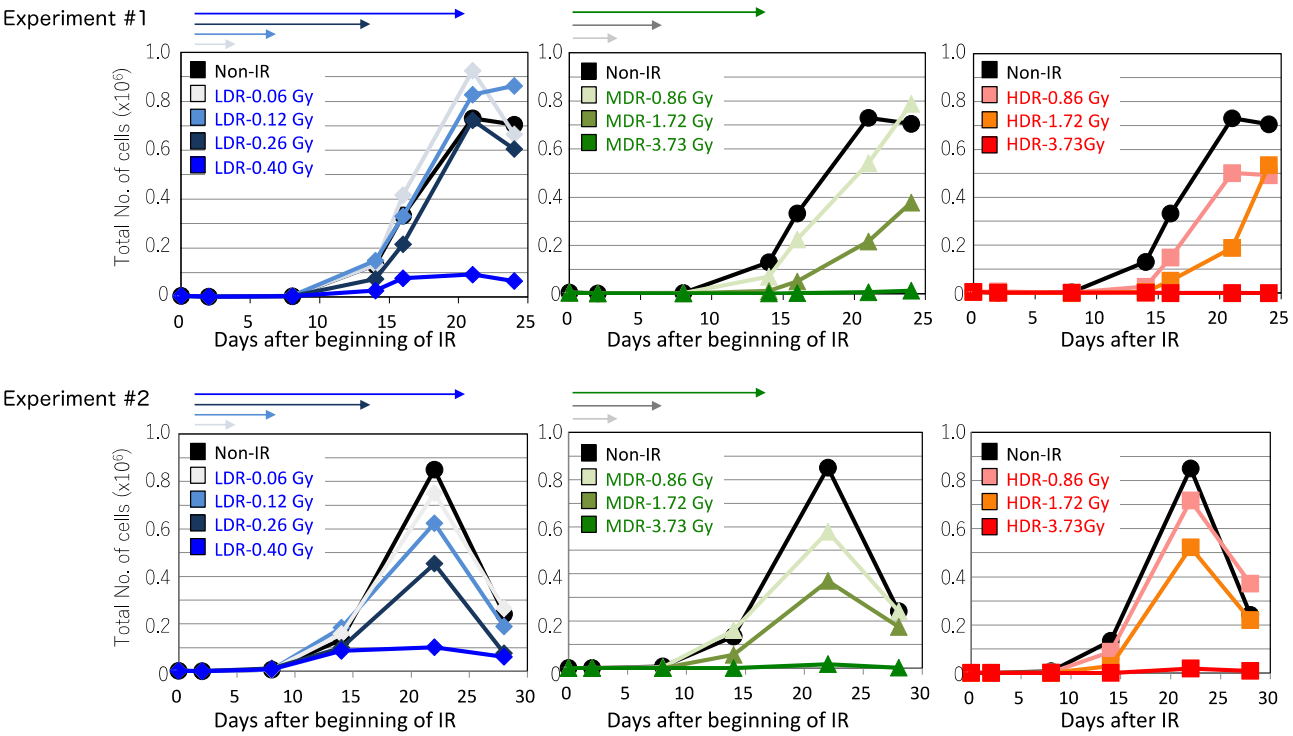

Fig. 1 Time-dependent changes in the number of *ex vivo*-cultured hematopoietic stem cells exposed to radiation (Experiments #1 and #2). Dose-rates of radiation were 839 mGy/min (HDR, high dose-rate), 287 mGy/day (MDR, middle dose-rate) and 20 mGy/day (LDR, low dose-rate). Dose rates and total doses are indicated near the symbols on the graphs. Arrows above the graphs indicate the irradiation periods of LDR- and MDR-irradiated groups. “Non-IR” means the non-irradiated group.