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EFFECT OF LOW DOSE RADIATION ON DIFFERENTIATION OF BONE MARROW CELLS INTO DENDRITIC CELLS

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□ Low dose radiation has been shown to be beneficial to living organisms using several biological systems, including immune and hematopoietic systems. Chronic low dose radiation was shown to stimulate immune systems, resulting in controlling the proliferation of cancer cells, maintain immune balance and induce hematopoietic hormesis. Since dendritic cells are differentiated from bone marrow cells and are key players in maintaining the balance between immune activation and tolerance, it may be important to further characterize whether low dose radiation can influence the capacity of bone marrow cells to differentiate into dendritic cells. We have shown that bone marrow cells from low dose-irradiated (γ-radiation, 0.2Gy, 15.44mGy/h) mice can differentiate into dendritic cells that have several different characteristics, such as expression of surface molecules, cytokine secretion and antigen uptake capacity, when compared to dentritic cells differentiated from the control bone marrow cells. These differences observed in the low dose radiation group can be beneficial to living organisms either by activation of immune responses to foreign antigens or tumors, or maintenance of self-tolerance. To the best of our knowledge, this is the first report showing that total-body low dose radiation can modulate the capacity of bone marrow cells to differentiate into dendritic cells.

Key Words: Low dose radiation, Dendritic cells, Immune system, Hematopoietic system, Hormesis

INTRODUCTION

Ionizing radiation has been established as a potent carcinogen. Extensive epidemiological studies of atomic bomb survivors showed that the incidence of solid cancer is significantly associated with radiation exposure. Moderate and high dose ionizing radiation can induce DNA strand breaks that may cause apoptosis and transformation into cancer cells and their risk is assumed to increase linearly with increasing radiation dose, with no threshold (the linear no threshold model: LNT model) (Huang *et al.* 2003; Preston *et al.* 2003). In contrast, the effect of low-dose ionizing radiation (< 0.2 Gy) is still controversial (Wall *et al.* 2006; Hoffmann and Stempsey 2008; Matsumoto *et al.* 2009). The radiation pro-

tection systems in most countries apply the LNT model even for low-dose ionizing radiation (< 0.2 Gy). However, some reports have shown that low dose ionizing radiation can be beneficial to living organisms, which is not consistent with the predicted data by the LNT model (Luckey 1982; Liu *et al.* 1987; Ishii *et al.* 1996; Iyer and Lehnert 2002; Ina *et al.* 2005). This may be explained by the fact that the LNT model is mainly based on the results of studies performed using moderate and high dose ionizing radiation. Thus, more studies may be required to elucidate the effect of low dose ionizing radiation and the related molecular mechanisms.

Dendritic cells (DCs) are professional antigen-presenting cells, unique in their ability to prime naïve T cells (Inaba *et al.* 1990). In general, homeostasis of most types of dendritic cells relies on continuous input from bone marrow cells (Merad and Manz 2009). Progenitor cells enter spleen, lymph node and mucosa-associated lymphoid organ and differentiate into dendritic cell subtypes. Co-stimulatory molecules such as CD80 and CD86 and MHC class molecules are essential for antigen presentation and T cell activation and their expression is associated with dendritic cells differentiation and maturation. These surface molecules and cytokines secreted during Dendritic cells maturation play important roles in the initiation of immune responses as well as in the maintenance of self-tolerance.

Previous studies have demonstrated the stimulating effects of low dose radiation (termed 'hormesis') on the immune and hematopoietic systems (Zhang *et al.* 2010; Liu *et al.* 1987; Li *et al.* 2004; Ina and Sakai 2005; Lacoste-Collin *et al.* 2007). Chronic low dose radiation was shown to stimulate immune systems, resulting in controlling the proliferation of cancer cells, maintain immune balance and induce hematopoietic hormesis, such as hematopoietic progenitor cell proliferation and peripheral blood mobilization. Since dendritic cells are differentiated from bone marrow cells and are key players in the induction of immune responses, it may be important to investigate the effect of low dose radiation on the differentiation of bone marrow cells into dendritic cells. Thus, we characterized the dendritic cells differentiated from the bone marrow cells of low dose-irradiated mice. We have shown that bone marrow cells of low dose-irradiated mice can differentiate into the dendritic cells with characteristics that are different from dendritic cells differentiated from the control bone marrow cells. To the best of our knowledge, this is the first report showing that low dose total body radiation can modulate the capacity of bone marrow cells to differentiate into dendritic cells.

MATERIALS AND METHODS

Mice

Male BALB/c mice (6~8-week-old) were purchased from the Central Lab. Animal Inc. (Seoul, Korea), kept under specific pathogen-free (SPF)

conditions in the animal facility of DIRAMS and used in accordance with the Institutional guidelines for Animal Care and Use Committee (IACUC).

Radiation Schedule

Continuous total-body irradiations were performed at the SPF conditioned irradiation facility using a ^{137}Cs irradiator (185 GBq) in DIRAMS. Mice were placed in cages on shelves, which were set at different distances from the irradiator to obtain the proper dose rates (1m: 15.44 mGy/h, 2m: 3.95 mGy/h and 3m: 1.818 mGy/h). After the completion of irradiation, mice were retuned to the cages in rooms without an irradiator and rested.

Reagents and antibodies

Recombinant mouse (rm) Granulocyte macrophage-colony stimulating factor (GM-CSF) and Interleukin-4 (IL-4) were purchased from R&D Systems (San diego, CA, USA). Lipopolysaccharide (LPS, from *Escherichia coli*055:B5) was obtained from Sigma-aldrich (St. Louis, MO, USA). The following FITC- or PE- or APC-conjugated monoclonal Abs were purchased from BD Biosciences (San Jose, CA, USA): CD3, CD4, CD8, CD19, CD45R (B220). The following FITC- or PE-conjugated monoclonal Abs were purchased from e-Biosciences (Sandiego, CA, USA): CD11c, CD80, CD86, MHC I, MHC II. Cytokine ELISA kits for murine IL-12 and IL-10 were obtained from R&D Systems (San diego, CA, USA). Fluorescein Isothiocyanate-Dextran (FITC: molecular mass, 40,000) was purchased from Sigma-aldrich.

Generation of BM-derived murine dendritic cells

Dendritic cells were generated from murine bone marrow cells according to a previously described method with minor modifications (Inaba *et al.* 1992). Bone marrow (BM) cells were flushed from the tibiae and femurs of BALB/c mice and depleted of RBC with RBC lysing buffer (Sigma-aldrich). The cells were plated in 6-well culture plates (10^6 cells/ml; 3 ml/well) in RPMI1640 supplemented with 10% heat-inactivated FBS, 2 mM L-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin, 50 μM 2-mercaptoethanol (2-ME), 10 mM 4-(2-hydroxyethyl)-1-piperazineëthanesulfonic acid (HEPES) (pH 7.4), and 20 ng/ml rm GM-CSF and rm IL-4 at 37°C and in a 5% CO_2 incubator. On day 3 of culture, floating cells were gently removed, and fresh complete medium was added with 20 ng/ml rm GM-CSF and rm IL-4. On day 6 of culture, non-adherent cells and loosely adherent proliferating dendritic cell aggregates were harvested for analysis or stimulation.

Flow cytometric analysis

Splenocytes and dendritic cells were harvested and washed with PBS and resuspended in FACS buffer (PBS w/ 0.5% FBS, 0.09% sodium azide). The cells were stained with the indicated antibodies conjugated with fluorescences (FITC, PE or APC) for 30min at 4°C, fixed and analyzed using a FACSAria II (Becton Dickinson, San Jose, CA, USA).

Antigen uptake assay

Briefly, dendritic cells (2_10^5 cells/ml) were pulsed with FITC-conjugated Dextran (1 mg/ml) at either 37°C or 4°C. At the indicated time points, the cells were harvested, washed 3 times with cold PBS and stained with PE-conjugated anti-CD11c Abs for 30 min at 4°C. Finally, cells were fixed with 4% paraformaldehyde and then analyzed using a FACSAria II.

Cytokines assay

Supernatants of dendritic cell culture were analyzed using ELISA kits for murine IL-12 and IL-10 (R&D system) according to the manufacturer's instructions. Levels of cytokine, chemokine and growth factors in serum were measured by a Luminex (Luminex, Austin, TX, USA) using Mouse cytokine/chemokine kit (MILLIPLEX map, Millipore, Billerica, MA, USA).

RESULTS

Total body low dose radiation (0.2 Gy) can induce molecular and cellular changes in vivo.

First, we evaluated whether low dose radiation (0.2 Gy) can generate changes at the molecular and cellular levels. Balb/c mice (male, 6~7 week-old) were irradiated at dose rates of 1.82, 3.95 or 15.44 mGy/h to reach a cumulative dose of 0.2 Gy. 1 day and 3 days after the completion of irradiation, peripheral blood mononuclear cells (PBMCs) were obtained from the blood of the control and the irradiated groups and then subjected to western blot analysis with antibodies to PARP, γ-H2AX and p53, which are well known markers of DNA damage. Low dose radiation increased the expression levels of PARP1 and p53 and phosphorylation of γ-H2AX (Phospho S139), suggesting that 0.2 Gy of total body radiation induced mild DNA damage responses in PBMCs. The dose rate of 1.82 mGy/h induced the expression of these proteins with slightly different time kinetics (Figure 1a). At dose rates of 3.95 and 15.44 mGy/h, PARP1 expression and phosphorylation of γ-H2AX increased at day 1 after the completion of radiation. However, at the dose rate of 1.82 mGy/h, expression only increased at day 3 after the completion of radiation.

The splenocytes from the mice irradiated (0.2 Gy, dose rate = 15.44) were prepared at day 1 after the completion of radiation and the relative population of B, CD3, CD4 and CD8 T cells was compared with that of the control mice. Even though there was no significant change in the B cell (B220$^+$CD19$^+$) population, the population of CD3$^+$ cells, including CD4 and CD8 T cells, in the spleen was increased by low dose radiation when compared to that of the control mice (Figure 1b). These results suggest that total-body low dose (0.2 Gy) radiation can induce in vivo changes at molecular (DNA damage response in PBMCs) and cellular levels (cell populations of spleen).

Low dose radiation increased co-stimulatory and MHC molecules on the surface of dendritic cells differentiated from bone marrow cells

Since 0.2 Gy of total body irradiation can induce in vivo changes at molecular and cellular levels, it may generate some effects on cells of other organs, including bone marrow. Dendritic cells differentiated from bone marrow cells play key roles in generating immune responses. Previous results showed that low dose radiation stimulated immune systems and induced hematopoietic hormesis (Zhang *et al.* 2010; Liu *et al.* 1987; Li *et al.* 2004; Ina and Sakai 2005; Lacoste-Collin *et al.* 2007). Thus, we investigated whether low dose radiation had an effect on differentiation of bone marrow cells into dendritic cells. Balb/c mice (male, 6~7 week-old) were irradiated at a dose rate of 15.44 mGy/h to reach a cumulative dose of 0.2 Gy, and 9 days after the completion of radiation, bone marrow cells were obtained, differentiated into dendritic cells with GM-CSF and IL-4 and matured with LPS (Inaba *et al.* 1992). CD11c-positive cells were gated and surface expression of CD80, CD86, MHC class I and II was evaluated by FACS analysis (Figure 2b). CD80 and CD86 are involved in co-signaling pathway and MHC class I and II play important
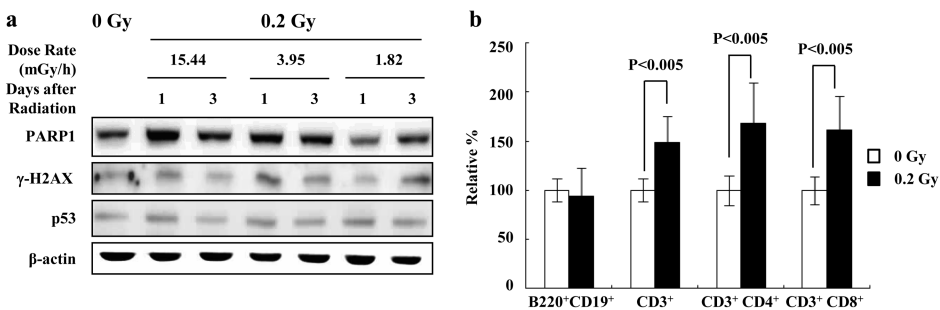

FIGURE 1. Changes at the molecular and cellular levels by low dose radiation. a) Mice were irradiated at a cumulative dose of 0.2 Gy at different dose rate (1.82, 3.95 or 15.44 mGy/h), PBMCs were isolated from the blood at day 1 and 3 after the completion of radiation. Western blot analysis was performed with the indicated antibodies. b) Mice were irradiated at a cumulative dose of 0.2 Gy at a dose rate of 15.44 mGy/h, splenocytes were prepared at day 1 after the completion of radiation and cell population was evaluated by FACS analysis.

roles in antigen presentation. Surface expression of CD80 and CD86 both on immature and mature dendritic cells was significantly increased by 0.2 Gy radiation compared to those of the control group. In the case of MHC class I and II molecules, their surface expression after 0.2 Gy radiation was also increased even though this increase was relatively low compared to that of CD80 & CD86. Thus, low dose total body radiation produced some effects on bone marrow cells, resulting in an increase in the level of surface molecules on BM cell-derived dendritic cells, which may be involved in the induction of immune responses.

Low dose radiation appeared to modulate antigen uptake capacity and cytokine secretion favorable for the immune tolerance

Even though co-signaling and MHC molecules of dendritic cells play central roles during the induction of immune responses, other functions of den-
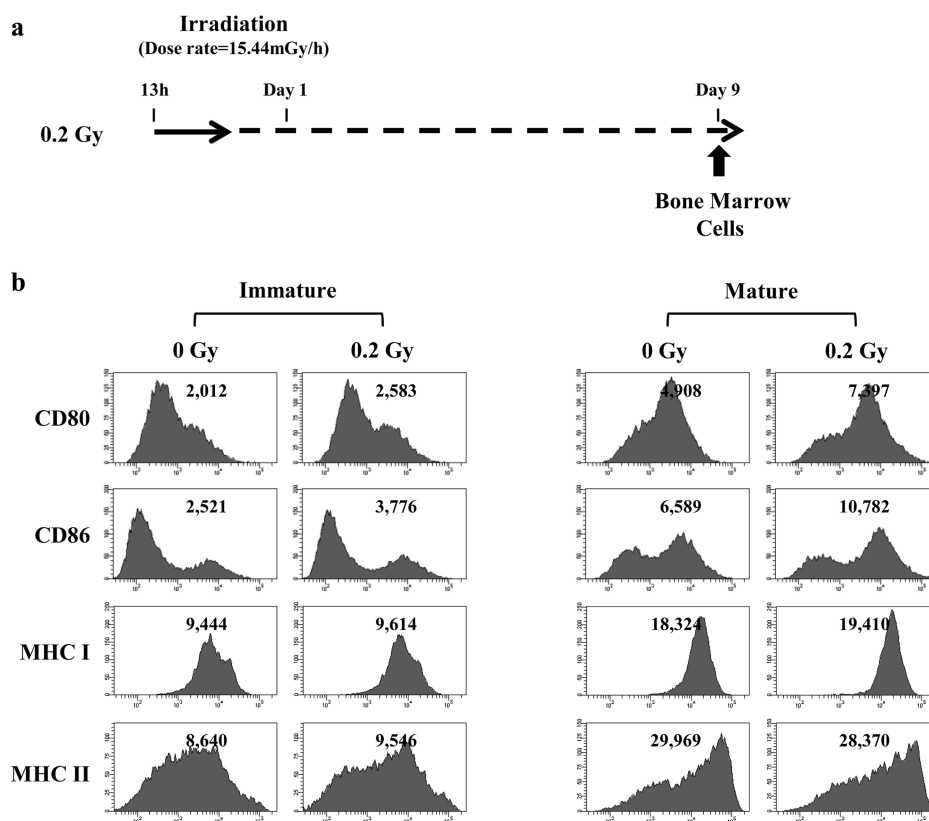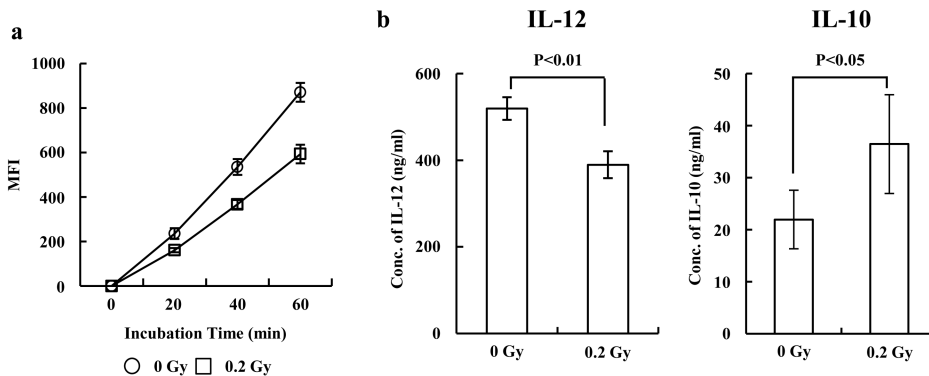

FIGURE 2. Effect of low dose radiation on the differentiation of bone marrow cells into dendritic cells. a) Experimental schedule is shown. b) Mice were irradiated with a cumulative dose of 0.2 at a dose rate of 15.44 mGy/h. Bone marrow cells were obtained and differentiated into dendritic cells (immature). Dendritic cell maturation was induced with LPS (200ng/ml). Expression of CD80, CD86, MHC I and MHC II of CD11c+ population was evaluated by FACS analysis.

dritic cells are also important for optimal immune inductions such as the antigen uptake capacity and proper cytokine secretion. Therefore, we compared these two functions between the control and the irradiated groups. BM cells from the control and the irradiated mice were differentiated into dendritic cells and used in the antigen uptake assay or further matured with LPS for cytokine analysis. The antigen uptake capacity was evaluated by FACS analysis using FITC-conjugated Dextran (Sallusto *et al.* 1995; Lee *et al.* 2007). In contrast to the surface expression of co-signaling and MHC molecules, the antigen uptake capacity of the dendritic cells derived from BM cells of the low dose-irradiated mice was lower than that of the control mice (Figure 3a). Cytokines, IL-10 & IL-12, secreted during dendritic cell maturation were evaluated by ELISA analysis. Supernatants were obtained after maturation with LPS and used to measure IL-12 and IL-10 levels, which are key cytokines for modulating the induction of naïve T cell activation. IL-12 secretion was decreased and IL-10 secretion was increased from dendritic cells derived from BM cells of the low dose-irradiated mice when compared to those of the control mice (Figure 3b). The pattern of cytokine secretion suggests that low dose radiation shifted the balance to tolerance in dendritic cell-mediated immune responses. Taken together, the antigen uptake capacity and the pattern of cytokine secretion of the irradiated group appeared to shift the balance to tolerance in dendritic cell-mediated immune responses.

Low dose radiation changed serum levels of G-CSF and IL-10

Since low dose radiation (0.2 Gy) induced changes in lymphocytes (molecular and cellular levels) and also in the capacity of BM cells to dif-
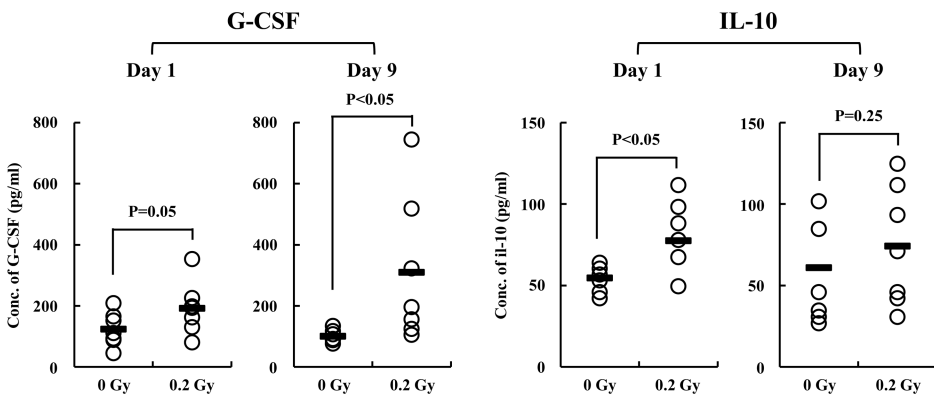

FIGURE 3. Effect of low dose radiation on the antigen uptake capacity and cytokine secretion of bond marrow-derived dendritic cells. a) Immature dendritic cells differentiated from bone marrow cells were incubated with FITC-conjugated Dextran (1 mg/ml) at 4 and 37°C. At the indicated time points, cells were harvested, washed with cold PBS three times and stained with anti-CD11c antibody. Uptake of FITC-conjugated Dextran by CD11c+ population was evaluated by FACS analysis. The background (MFIs from dendritic cells incubated at 4 °C) was substracted. MFI: Mean Fluorescence Intensity. b) Immature dendritic cells differentiated from bone marrow cells were matured with LPS (200ng/ml) for 24 hrs. The supernatant was collected and the levels of IL-12 and IL-10 were measured.

ferentiate, there may be changes in modulators such as cytokines, chemokines and growth factors. Thus, we have evaluated the levels of cytokine, chemokine and growth factors in serum using Luminex assay. Serum was prepared at day 1 and 9 after the completion of radiation and subject to Luminex assay to measure 32 cytokine, chemokine and growth factors simultaneously. The levels of several factors were under detection limit and those of others were not statistically different between the groups (data not shown). However, there were some factors whose serum levels appeared to be significantly different between the groups, such as G-CSF and IL-10 etc. The serum levels of G-CSF and IL-10 were increased at day 9 and at day 1, respectively, in the 0.2 Gy-irradiated group (Figure 4). G-CSF is known to play important roles in mobilization of bone marrow stem cells and IL-10 has several effects in immune-regulation and anti-inflammation. Thus, low doe radiation (0.2) may induce changes at serum levels of cytokines such as G-CSF and IL-10 and then these factors may influence the hematopoietic and immune systems. Although other factors were under the detection limit and were not statistically different between groups in this study, it is still possible that others also can be modulated by low dose radiation.

DISCUSSION

The international Commission on Radiological Protection (ICRP) proposes that damage caused by radiation increases in a dose-dependent manner with no threshold dose, which is the so-called linear no threshold (LNT) model. However, the effect of low dose radiation is still controversial. Since the immune system is one of the most sensitive biological sys-

FIGURE 4. Effect of low dose radiation on the serum levels of G-CSF and IL-10. Mice were irradiated with a cumulative dose of 0.2 at a dose rate of 15.44 mGy/h. Blood was taken and serum was prepared at day 1 and 9 after the completion of radiation. Levels of cytokine, chemokine and growth factors in serum were measured by a Luminex. Open circle: the serum level of each cytokine in the individual mouse, bar: the average of the group.

tems to radiation, many researchers have used the immune system to evaluate the effects of low dose radiation. The hematopoietic system has also been widely used to evaluate the effect of low dose radiation. It was reported that low dose radiation induced hematopoietic hormesis, such as hematopoietic progenitor cell proliferation, peripheral blood mobilization and hematopoietic reconstitution (Zhang *et al.* 2010; Li *et al.* 2004). Thus, it may be interesting to determine if low dose radiation affects the capacity of bone marrow cells to differentiate into dendritic cells. In that way, we may evaluate simultaneously the effect of low dose radiation on the hematopoietic system and the secondary effects on the immune system since dendritic cells are key players in balancing immune induction and tolerance maintenance to self. Dendritic cells differentiated from the bone marrow cells o'f the low dose-irradiated mice resulted in enhanced expression of co-signaling and MHC molecules compared to the control group. In the absence of systemic damage, low dose radiation may be beneficial since the enhanced expression of co-signaling and MHC molecules can result in enhanced immune responses to foreign pathogens and tumors.

The effect of low dose radiation on cytokine secretion and antigen uptake capacity of dendritic cells appeared to be different from that on surface molecules. In terms of cytokine secretion during dendritic cell maturation, IL-12 was decreased and IL-10 was increased in the low dose radiation group when compared to the control group. This pattern of cytokine secretion may imply a shift to immune tolerance rather than immune activation. This may be the case because low dose radiation can induce cell death even in a small population (Matsubara *et al.* 2000). Thus, the immune and the hematopoietic systems need to prevent immune activation to self. This is consistent with the results of the antigen uptake assay, where immature dendritic cells differentiated from the bone marrow cells of the irradiated groups showed lower antigen uptake capacities compared to the control. The results of cytokine secretion analysis and antigen uptake assay suggest that low dose radiation modulates the immune and hematopoietic system to prevent autoimmunity.

Two phenomena induced by low dose radiation appeared to be contradictory. Enhanced expression of co-signaling and MHC molecules is associated with enhanced immune responses but reduced IL-12, enhanced IL-10 secretion and reduced antigen uptake capacity is associated with immune tolerance. However, accumulating data suggest that several types of dendritic cells may exist, which do not fit into the bimodal concept of immature versus mature dendritic cells (Lutz and Schuler 2002; Yamazaki *et al.* 2006; Hubert *et al.* 2007). One of them is the semi-immature dendritic cells, which display upregulated co-signaling and MHC molecules and no IL-12 production. These phenotypes are similar to those of the dendritic cells differentiated from the bone marrow cells

of the low dose-irradiated mice in our study. They express enhanced co-signaling and MHC molecules compared to those of the control and do not secret IL-12 before LPS stimulation. When considering the reduced antigen uptake capacity, they may shift the balance to the maintenance of tolerance. In that way, our bodies can inhibit immune activation, which may be stimulated by inflammation due to the apoptotic bodies of irradiated cells. This should be the subject of further studies. In addition, we must also measure and characterize the immune responses to either foreign or self antigens. Depending on the circumstance such as types of antigens or danger signals, two different phenomena may differentially contribute to the immune system, resulting in immune activation or maintenance of tolerance.

Low dose radiation induced changes in serum levels of G-CSF and IL-10. These factors may influence the hematopoietic and the immune systems since these systems are generally regulated by cytokine, chemokine and growth factors. Although other factors were not statistically different between the groups and their serum levels were under detection limit in our study, it still possible that low dose radiation may modulate other cytokine, chemokine and growth factors to have effects on the hematopoietic and the immune systems. This may need to be further characterized if more sensitive analytic methods are available.

In conclusion, we showed that total body low dose radiation can affect the capacity of bone marrow cells to differentiate into dendritic cells, which displayed different characteristics when compared to the control. To the best of our knowledge, this is the first report showing the effect of total body low dose radiation on the capacity of bone marrow cells to differentiate into dendritic cells.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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