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Protective Effects of Ginsenosides Rb2 on Irradiation-Induced Hematopoietic System Injury in the Mice

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Abstract: Ginsenosides Rb2 is an extract of ginseng which has a broad range of therapeutic and pharmacological applications. This study, aimed to explore the protective effects of Rb2 on irradiation-induced hematopoietic system injury in mice. The Rb2 was administrated twice a day to the mice for 3 days and mice were irradiated for 10 Gy after the last injection. The weight and the activity of the mice were evaluated daily. On day 14 after irradiation, blood cell counts were analyzed. It was found that Rb2 alleviated radiation-induced changes in blood cell counts. Compared with irradiation alone group, mice in Rb2 group showed better behaviors. Ginsenosides Rb2 may be a beneficial agent against radiation-induced blood system damage.

Key words: Ginsenoside Rb2, radiation, hematopoietic

INTRODUCTION

Radiotherapy is one of the common treatments for a wide variety of malignant tumor (Hogle, 2006). Approximately 50% of the patients with malignant tumor need to accept radiotherapy and more than 70% of the patients with malignant tumor undergo radiotherapy in the United States (Dainiak *et al*., 2003). However, radiotherapy is used mostly for patients with advanced cancer, as a result of the normal tissue damage caused by radiotherapy. Moreover, radiotherapy could increase the risk of cancer and lead to tumor recurrence in some patients (Cannon and Lee, 2008). Therefore, radiation protection of normal tissues in radiotherapy is one important problem to be solved.

Hematopoietic tissue in the spinal cord is a string-shaped arrangement tissue. X-ray radiation, neutron and gamma can directly damage blood stem cell and bone marrow microenvironment. In the short term, patients have symptoms such as fatigue, weakness, prone to infection, the signs and symptoms of infection are often not obvious. However, the infection is progressing very quickly with high mortality. Therefore, the prevention of radiation damage to hematopoietic system is an effective means to increase the radiation dose and improve the quality of life of patients.

Ionizing radiation often causes irreversible damage and even death to normal tissue cells because of free radicals attacking DNA in the nucleus. Ginseng is one of the most widely used herbal medicines and has a broad range of therapeutic and pharmacological applications (Cheng *et al*., 2013). The ginseng is composed of 2-3% ginsenosides. The Rb1, Rb2, Rg1, Rc, Rd and Re are the most important extracts among more than 30 different kinds of ginsenosides. Ginsenosides Rb2 is a ginseng extract which could increase immunity and promote DNA repair. In this study, the effect of ginsenosides Rb2 on hematopoietic system in mice exposed to radiation was observed and the potential of ginsenosides Rb2 in the auxiliary function of radiation therapy was explored.

MATERIALS AND METHODS

Animals: Eight week-old male ICR mice were purchased from Animal Center of Nantong University. The animals were maintained in a room at 25°C with humidity of 50%. The animals were kept in a daily light-dark cycle with free access to food and water *ad libitum*.

The animals were randomized to the following three groups: (1) Control group which were non-irradiated and received intragastric administration of 200 μL 0.9% saline; (2) Irradiation alone group which received intragastric

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administration of 200 μL 0.9% saline twice daily for 3 days followed by exposure to Whole Body Irradiation (WBI) at a dose of 10 Gy; (3) Experimental group which received intragastric administration of 200 μL Rb2 (purchased from Nanjing Guangrun Biological Products and dissolved in 0.9% saline at 15 μg mL^{-1}) twice daily for 3 days followed by exposure to WBI at a dose of 10 Gy. There were 6 mice in each group and they were sacrificed 7 and 14 days after radiation exposure. Specimens were collected and the weight and activity, spirit, fur of mice were recorded at the same time every day.

Irradiation: Mice were placed in ventilated plastic containers and received whole-body irradiation using six MV high-energy X-rays (WARIAN, 23EX, America) with a dose of 10 Gy, 400°C Gy min^{-1}. The source-to-skin distance was 100 cm and the radiation field was 20×20 cm.

Haematological measurements: Blood samples (0.8 mL) were obtained from eyeball of anesthetized animals. Peripheral blood cell count such as White Blood Cell (WBC), Red Blood Cell (RBC) and platelet counts and hemoglobin concentration was determined by using an auto-mated hematology analyzer (Sysmex Co., XE2100, Japan).

Statistical analysis: Data was presented as Mean±SD. The p-value <0.05 was considered statistically significant. Multiple factor randomized analysis of variance was used to compare the difference among parameters.

RESULTS

Activity of the mice in each group: Two days after irradiation, mental deterioration, reduced activity and decreased food intake, as well as weight loss in the mice of IR alone group were observed. The hair of mice was dim and dark and easy off. Obvious infection and bleeding appeared 7 days after irradiation. In contrast, the activity of mice in Rb2 group was slightly higher than that of IR alone group, particularly 7 days after irradiation. In Rb2 group, the hair of mice was lustrous and smooth, with no obvious symptoms of infection.

Body weight of the mice in each group: Body weight of animals in each group was shown in Fig. 1. In control group, the body weight increased gradually from 27.00±1.26 g on Day 0 to 34.87±1.55 g on Day 14. In IR alone group, body weight of mice gradually increased but showed a gradual decline four days after irradiation, from 28.33±1.63 g on Day 0 to 20.15±0.35 g on Day 14. In contrast, the body weight of mice in IR group gradually recovered in Rb2 group, from 22.38±2.57 g on Day 4 to 28.33±1.56 g on Day 14. On the 14th day after irradiation, mice died in IR group but mice in the other two groups survived.

Hematological parameters of the mice in each group: The hematological parameters of the mice in each group were analyzed by automatic blood analyzer. As shown in Fig. 2, WBC counts ($\times 10^9$ L^{-1}) were 8.67±1.22, 0.16±0.06, 2.26±0.54 in Control, IR and Rb2 group on Day 7, respectively and 8.83±1.44, 1.08±0.38, 4.18±0.77 in Control, IR and Rb2 group on Day 14, respectively. For RBC counts ($\times 10^{12}$ L^{-1}), they were 5.21±2.95, 3.16±0.24 and 4.08±2.67 in Control, IR and Rb2 group on Day 7, respectively and 4.62±1.41, 3.57±0.67 and 5.19±0.94 in Control, IR and Rb2 group on Day 14, respectively. For platelet counts ($\times 10^9$ L^{-1}), they were 278.1±50.46, 48.5±19.85 and 112.8±34.59 in Control, IR and Rb2 group on Day 7, respectively and 222.30±36.93, 84.85±37.72 and 139.70±45.51 in Control, IR and Rb2 group on Day 14, respectively. For HB concentration (g L^{-1}), it was 122.70±21.49, 85.17±17.34, 107.20±3.97 in Control, IR and Rb2 group on Day 7, respectively and 132.00±18.73, 98.67±26.40, 119.70±19.39 in Control, IR and Rb2 group on Day 14, respectively.

Compared to control group, WBC counts and platelet counts significantly decreased in IR group on Day 7 or 14 post-irradiation ($p<0.05$), especially for WBC counts they dropped to a very low level. Nevertheless, WBC count increased significantly in Rb2 group. In addition, RBC counts and HB concentration were slightly higher in Rb2 group.

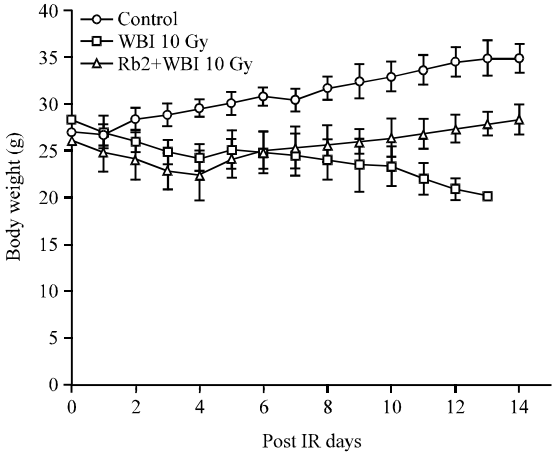

Fig. 1: Changes in body weight of the mice for 14 days in all groups. Data was presented as Mean±SD (n = 6)

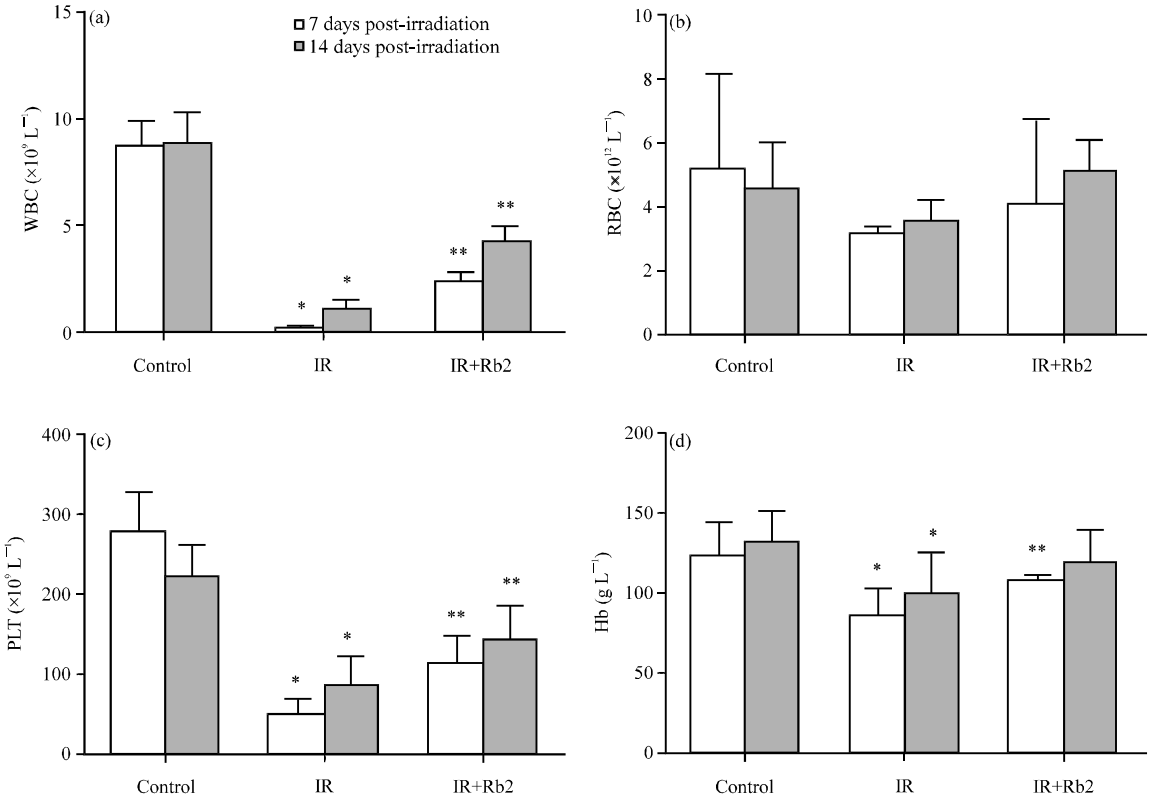

Fig. 2(a-d): Hematological indices of the mice in all groups. (a) WBC counts, (b) RBC counts, (c) Platelet counts and (d) Hemoglobin concentration. Data was presented as Mean±SD (n = 6), **p<0.05 vs. IR group. *p<0.05 vs. control group

DISCUSSION

Ionizing radiation is toxic to organisms because it induces deleterious structural changes in essential macromolecules in the body, such as DNA, proteins and enzymes. It is known that the exposure to irradiation could damage the blood system. The radiation-induced hematologic system has been investigated extensively in recent years (Chen *et al*., 2006). The low number of peripheral blood leucocyte renders the patients vulnerable to potentially life-threatening infections (Horwitz *et al*., 1999). Studies of radiation accidents indicated that the hematologic system can not recover to normal levels (Galotto *et al*., 1999).

Ginsenoside Rb2 is one of the richest subtypes in more than 30 kinds of ginsenosides which have multiple biological roles including antioxidative function (Shim *et al*., 2010; Joh *et al*., 2011; Theilgaard-Monch *et al*., 2005; Ramesh *et al*., 2012). Ginseng was a potential radioprotectors (Hosseinimehr, 2007; Raghavendran *et al*., 2012). Ginseng recovered the radiation-induced changes in blood cell counts, including white blood cells and red blood cells counts (Kwon *et al*., 2000). Several studies showed that the administration of ginseng protected the mice from radiation (Liang *et al*., 2013). In addition, ginseng extract as well as its fractions significantly increased endogenous spleen colony formation in mice after irradiation (Cai *et al*., 2009).

The present results demonstrated that Rb2 improved the survival of irradiated mice. Damage in the intestine was less severe in irradiated mice treated with Rb2 than in those treated with saline alone. Growing evidence from radiation accidents and other physical insults has indicated that hematopoietic system injury induced by irradiation plays a key role in the process of the development of multi-organ involvement and in the survival of patient. In the present study, the survival of mice administered with Rb2 or saline during irradiation was observed. These results demonstrated that treatment with Rb2 reduced the mortality rate of mice.

CONCLUSION

In conclusion, Rb2 reduced radiation-induced changes in blood cell counts. Compared with irradiation alone group, mice in Rb2 group showed better behaviors.

Therefore, we propose that Rb2 is a candidate for adjuvant therapy to alleviate radiation-induced injury to blood system.

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