Radiation-induced Biological Response against Low Dose and Low Dose Rate of Irradiations

W09–1 Role of p53 Gene in Apoptotic Repair of Genotoxic Tissue Damage in Mice
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Tissue repair is specific to multicellular organisms. It has been experimentally established with mice that embryonic or fetal cells are extremely sensitive to killing by ionizing radiation. I will present evidence that the hypersensitivity of these cells is due to deletion of damaged cells in tissue by apoptosis. After gamma-irradiation of p53(+/+) mice with 3 Gy, the mutation frequency of mice T-lymphocytes defective in T-cell receptor (TCR) gene expression was considerably higher than the control level for acute exposure (1020 mGy/min). However, when an equal dose of 3 Gy was given but at a lower dose-rate (1.2 mGy/min), the frequency of mutant T-lymphocytes did not increase at all for p53(+/+) mice which are capable of p53-dependent apoptosis, whereas the dose of 3 Gy remained mutagenic for p53(−/−) mice unable to carry out p53-dependent apoptosis. These results indicate that p53 deficiency should lead to an increased mutation frequency, either by failure to permit repair of damaged DNA or by failed deletion of mutation bearing cells. Hence, complete repair of genotoxic damage requires the two mechanisms, p53-dependent apoptotic tissue repair as well as the well-known DNA repair.

W09–2 Pre-irradiation with a Low-dose-rate Enhanced DNA-PK Activity and Then Depressed Radiation-induced Apoptosis
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Studies of molecular mechanisms are quite important to clarify for radioadaptation. Using Scid mouse deficient DNA-PKcs, we examined the role of DNA-PK activity in radioadaptation. When the wild-type mice were previously exposed to chronic irradiation (1.5 Gy) with low-dose rate (1 mGy/min), the induction of Bax and apoptosis by acute irradiation (3 Gy, 1 Gy/min) was significantly suppressed especially in splenic white pulp of the mice. However, it was not changed by acute irradiation immediately after pre-irradiation with low-dose rate in Scid mice, although we detected it in spleen after acute irradiation alone. These data suggest that DNA-PK activity might act a major role on the radioadaptive response by irradiation with low-dose rate.
W09–3 Radio-adaptive response in whole animals
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We have reported two types of radio-adaptive survival response in mice. Pre-irradiation with 0.05 Gy induced radio-resistance (decrease in bone-marrow death) 2 months later, and pre-irradiation with 0.5 Gy induced radio-resistance 2 weeks later. In the latter case the radio-resistance occurred on day 9 and continued for 9 days, and the former radio-resistance continued for half a month. These results show that the radio-adaptive response in whole animals is distinctly different from that observed in the cell level, which continues less than 2 days after low dose irradiation. Biological effects of low dose (0.05–0.1 Gy) and small dose (0.5 Gy) were reported by Matsubara et al. on immune effects. The time at the augmentation of T-cell dependent immune responses coincided with the time at the induction of the two types of acquired radio-resistance. Effects of pre-irradiation after challenging high-dose irradiation have been observed as decreased hemorrhage, stimulated (but rather small) recovery of blood cell counts. Decrease in p53 induction as well as apoptosis in the spleen has been observed in a co-work with Prof. Ohnishi, Nara Med. Univ. We are obtaining results on the stimulated recovery of endo-CFUs by the pre-irradiation with 0.5 Gy.

W09–4 Radon Effects and Thermal Effects on Humans in Radon Therapy
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The effects of the radioactivity of radon and thermal effects were compared under the condition with the same chemical effects. In the result, the activity of SOD, which is an oxidation inhibitor, was significantly increased, and the levels of LPO and LDL-cholesterol, which are closely involved in arteriosclerosis, were significantly decreased on days 6 and 7. The results were about 2-fold larger in the radon group than in the thermo group. This suggests that the antioxidation function was more enhanced by radon therapy than by thermo therapy, and suggested that radon therapy may prevent the causes of life style-related diseases such as arteriosclerosis. These findings are important in understanding the mechanism of diseases to which radon therapy can be performed and most of which are called activated oxygen-related diseases.

W09–5 Enhancement of TNF Production of Macrophages by Continuous Gamma-Ray Irradiation
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Biological effect of radiation is dose-dependent, and it is known that low dose radiation have beneficial effects on host and cells as proposed by Lucky et al. as hormesis, even if high dose radiation impairs cellular functions and proliferation. Here we studied the effects of continuous gamma-ray irradiation on cellular functions to elucidate molecular mechanisms of hormesis. Less than 1.4 mGy/h had effect neither on the number of peripheral white cells, and weights of thymus and spleen of whole body irradiated mice, nor on p53 activity and proliferation of human osteosarcoma. We found that such low dose-rate irradiation enhanced TNF production of inflammatory macrophages stimulated with LPS. The enhancement was observed at as low as 50 µGy/h, and specific for TNF production of macrophages. We also observed transcription enhancement of TNF gene, and degradation of IkB which regulates transcription of TNF. These results suggest that macrophages respond most sensitively to low dose-rate radiation and that transcription activation of NFκB plays an important role in the expression of hormesis.
W09–6  
Elevation of Glutathione Induced by Low-dose γ-Rays and Its Involvement in Increased Natural Killer Activity
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Glutathione level in mouse splenocytes significantly increased between 2 h and 6 h after whole-body γ-ray irradiation at 0.5 Gy, peaked at 4 h, and thereafter decreased almost to the zero time (0 h) level by 12 h post-irradiation. A significant enhancement of NK activity was recognized in the splenocytes obtained from the whole-body-irradiated mice between 4 h and 6 h post-irradiation.

Reduced glutathione (GSH) exogenously added to splenocytes obtained from normal mice enhanced both total cellular glutathione content and the NK activity in a dose-dependent manner. Other precursors of de novo GSH synthesis, such as cysteine, N-acetylcysteine and oxidized glutathione also effectively increased the activity. These enhancements were completely blocked by buthionine sulfoximine, an inhibitor of de novo GSH synthesis.

These results suggest that the induction of endogenous glutathione in living cells immediately after low-dose γ-ray irradiation is at least partially responsible for the appearance of enhanced immune functions, including mitogenic response and NK activity.

W09–7  
Long-term Low-dose-rate Continuous Gamma-ray Irradiation on Mice -interim report-
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The purpose of the experiment is to evaluate the biological effects of low dose radiation based on the life span and neoplasm incidence. The experiment is currently in progress and is scheduled for completion in 2003. This interim report is based on the data these were collected from 1996 to the present.

A total of 4000 SPF B6C3F1 mice were divided into four groups [three irradiated groups and one control group], each consisting of 500 male and 500 female mice. Irradiation was performed using 137Cs gamma-rays at dose-rates of 20 mGy/day, 1 mGy/day and 0.05 mGy/day with accumulated doses equivalent to 8000 mGy, 400 mGy and 20 mGy, respectively. The life span of the mice dosed with 20 mGy/day is significantly shorter than that of control group. There is no significant difference in the relative frequency of occurrence of neoplasms between control and irradiated groups.

W09–8  
Suppressive Effect of Low Dose Rate Chronic Irradiation on Carcinogenesis
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Female ICR mice, 6 week-old, 35 in each group, were exposed to gamma-rays from a 137Cs source in the long-term low dose rate irradiation facility at CRIEPI. The dose rate was 2.6 mGy/hr (A), 0.96 mGy/hr (B), or 0.30 mGy/hr (C). Thirty-five days later, the mice were injected into the groin with 0.5 mg of methylcholanthrene (MC) dissolved in olive oil and irradiation was continued. Cumulative tumor incidences after 216 days following MC injection were 89% in group A, 76% in group B, and 94% in group C. That in non-irradiated control group was 94%. The difference in the tumor incidence between the control and position B was statistically significant, indicating the suppressive effect of the low dose rate irradiation on the process of MC-induced carcinogenesis with an optimum dose rate around 1 mGy/hr. Similar results were observed under an condition with a reduced concentration of MC.