# §25. Assessment Study on Biological Effects of Radiation in LHD

Ichimasa, Y., Tauchi, H., Tachibana, A. (Fac. Sci., Ibaraki Univ.),
Komatsu, K. (Rad. Biol. Center, Kyoto Univ.),
Kamiya, K. (RIRBM, Hiroshima Univ.),
Norimura, T. (Univ. Occupational & Environ. Health),
Takeda, H. (Natl. Inst. Rad. Sci., Chiba),
Ono, T. (Tohoku Univ. Graduate School of Med.),
Uda, T.

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In this study, we investigated on i) biological effects of low-dose (rate) tritium radiation, ii) establishment of hypersensitive assay system for radiation biological experiments, and iii) analysis of the mechanism of DNA damage response. Here we summarize the results obtained by this study.

i) Biological effects of low dose tritium radiation.

An exposure condition of tritium radiation from nuclear fusion reactor could be a long-term exposure at low dose rate. Regarding to mutation induction by high LET radiation such as neutrons, the reversed dose rate effect has been reported when the dose rate is lower than a certain value. It is not clear whether this phenomenon could be seen in the case of tritium radiation. To examine the low dose rate effect of tritium radiation, we established a hypersensitive mutation detection system using hamster cells carrying a human X-chromosome. We have tested mutation induction by tritiated water at dose rate between 0.13 and 4.4 cGy/h. Although mutation frequency seems to be slightly increased at lower dose rate tritium radiation, it was not statistically significant. Our results suggest that the reversed dose rate effect may not be seen for mutation induction by tritium radiation.

Ionizing radiation may affect not only individual organism but also the ecosystem. Therefore we also discussed about the effect of low dose tritium radiation on a simplified *in vitro* ecosystem, microcosm. To access the effect of low dose radiation on microcosm, *Euglena* were continuously irradiated at low dose. Interestingly, the cell number of *Euglena* was increased when the microcosm was irradiated at very low dose rate (about 0.5mGy/day). This suggests the existence of hormesis effects on cell growth of the *Euglena*.

ii) Establishment of hyper-sensitive assay system for radiation biological experiments.

The biological effects of low dose (rate) radiation are still unclear because none of suitable detection system, which gives us an objective and quantitative data, has ever been established before. To establish a novel experimental system that can examine the low dose rate effect of tritium radiation, we tested a hypersensitive mutation detection system for the both *in vitro* and *in vivo*. The *in vitro* system uses hamster cells carrying a human X-chromosome fro *Hprt* gene, and the *in vivo* system uses Rev1 (a error prone repair gene) transgenic mice.

In the *in vitro* system, any of somatic mutations or gene deletions in the human X chromosome do not affect cell viability when cells are cultured in normal medium. This system appears to be able to detect a wide spectrum of mutations, even mutations affecting the expression of important genes in the neighborhood of the *Hprt* gene. The system showed about 100-fold sensitivity compared to conventional system. The Rev1-transgenic mice also showed the high incidence of malignancy and this may be able to use as a “mammalian Ames test” to detect any mutagenic effects of DNA damaging agents.

We also investigated the apoptosis induction by tritium radiation in knockout mice for p53 tumor suppressor gene. It was suggested that p53 stimulates repair system and then protects the mice from mutagenesis by inducing apoptosis following DNA damage. These hyper-sensitive detection system should be useful for further investigation to obtain the experimental data for low dose (rate) exposure of tritium radiation.

iii) Analysis of the mechanism of DNA damage response

Radioadaptive response is a biological defense mechanism in which low-dose ionizing irradiation elicits cellular resistance to the genotoxic effects of subsequent irradiation. However, its molecular mechanism remains largely unknown. We have demonstrated that the dose recognition and adaptive response could be mediated by a feedback signaling pathway involving protein kinase C (PKC), p38 mitogen activated protein kinase (p38MAPK) and phospholipase C (PLC). Because DNA-damage repair proteins may also be related to this radioadaptive response, we are investigating molecular biology of DNA damage repair genes. We cloned the homolog of NBS1 protein in plants and found that the protein can be induced by X-ray exposure. This finding provides us a new aspect of DNA damage response in plants and similarity of the repair system between mammals and plants. Clarifying molecular mechanisms of radiation-induced DNA damage repair and of the adaptive response is one of the major subjects for our future study.

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