§42. Assessment Study on Biological Effects of
Low-dose Radiation

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An exposure condition of tritium radiation from
nuclear fusion reactor could be a long-term exposure at low
dose rate. In this study, we focused on i) establishment of a
hypersensitive assay system for radiation biological
experiments and ii) biological responses to low-dose (rate)
radiation, and iii) the mechanism of DNA damage response.
Followngs are summary of the results obtained in this
study.

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

The biological effects of low dose (rate)
radiation are still unclear because any experimental system,
which allows us to obtain quantitative data with low dose
radiation, has not been established. Therefore, we are
trying to establish a novel experimental system that can
evaluate the biological effects of low dose (rate) tritium
radiation, for the both in vitro and in vivo. In this study, we
established a hypersensitive mutation detection system
using hamster cells carrying human X chromosome. We
also tested availability of transgenic mice that carries a
mutation reporter gene, gpt-delta. Another transgenic mice
line that uses Rev 1, a error prone repair gene, also tested
their possibility to use as a hyper-sensitive system of
carcinogenesis.

In the human-X-carrying hamster cell system,
any somatic mutations and gene deletions in the additional
human X chromosome do not affect the cell viability when
cells are cultured in normal medium. This system appears
to be able to detect a wide range of mutation spectrum,
even if those mutations affect the expression of important
human genes for cell survival. The system showed about
100-fold sensitivity compared to the conventional system
that uses Hprt gene locating the internal X-chromosome.

Because the Rev1-transgenic mice showed the
high incidence of malignancy we are now testing the
possibility to use as a “mammalian Ames test” to detect
any mutagenic effects of DNA damaging agents.

Using p53 (a tumor suppressor gene) knockout
mice, we also investigated the induction of chromosomal
aberrations by tritium radiation. It was suggested that p53
stimulates repair system and suppress chromosomal
aberrations. Because p53 induces apoptosis after low dose
tritium uptake 1), it may protect the mice from mutagenesis
by both the activation of DNA damage repair and induction
of apoptosis. The p53-knockout mice could be useful to test
the in vivo effects of low dose tritium radiation. These
hyper-sensitive detection system will be further tested to
establish the experimental system for low dose (rate)
exposure of tritium radiation.

ii) Biological responses to low-dose (rate) radiation.

Radio-adaptive 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
recognition of primary-dose and adaptive response could be
mediated by a feedback signal pathway that involves
protein kinase C (PKC), p38 mitogen activated protein
kinase (p38MAPK), and phospholipase C (PLC). We have
started experiments to clarify the effect of PKC knockdown
by siRNA on radio-adaptive response. By the experiments,
we may verify the importance of PKC pathway for
expression of radio-adaptive responses.

iii) Analysis of the mechanism of DNA damage response

We are investigating molecular biology of DNA
damage repair genes. For example, NBS1 is a critical
protein for regulation and activation of DNA damage
response 2). We have established a reporter cell system for
homologous recombination repair and studied the effect of
NBS1 mutation on homologous recombination. We found
that the NBS1 regulating homologous recombination
through the regulation of nuclear localization and foci
formation of MRE11/RAD50 protein complex. Interestingly,
ATM, another critical regulator of DNA damage response,
was not essential for regulation of homologous
recombination. This suggests that ATM may functions on
radiation-damage specific end-processing or regulation of
non-homologous recombination that is known to be a major
pathway for DNA damage repair in mammalian cells 3).

   (in Japanese)