§31. A New Approach for Estimation of the Biological Effects of Low Level Tritium Radiation

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Tritium is planned to be as fuel for nuclear fusion reactions. In order to estimate the relative radiation risk from nuclear fusion plants, it is critical to understand the biological effects of low dose rate tritium exposure. However, the estimation of tritium risk has not been elusive. Therefore, the present study is focused on, i) analysis of biological effects of tritium by using genetically engineered animal model, ii) analysis of the biological effects of tritium by using culture cell line, iii) analysis of the molecular mechanism of tritium radiation-induced DNA damage response. The following presents a part of the results

i) Analysis of biological effects of tritium by using animal model

A loss of a GPI anchor protein corresponds to the mutation frequency which has occurred to the *Pig-a* gene on the X chromosome, and is considered to reflect the mutation which arose in the general body cell. We analyzed the mutation frequency of *Pig-a* gene induced by tritiated water (HTO) using mice.

CD24, one of the GPI anchor protein, negative erythrocyte began to increase at 15 days after g-ray irradiation or HTO inoculation, and the maximum was shown at 21 days after. The mutation frequencies were almost comparable at g-ray acute irradiation and HTO. On the other hand, the mutation frequency by HTO in the *TCR* gene which we reported before was about 50% of that by g-ray acute irradiation. Therefore, *Pig-a* gene assay seems more useful for the evaluation of influence of tritium than *TCR* gene assay.

ii) Analysis of the biological effects of tritium by using culture cell line

Radioadaptive response is a biological defense mechanism in which low-dose ionizing irradiation, such as the treatment with low concentration of tritiated compounds, gives cellular resistance to the genotoxic effects of high-dose ionizing irradiation. We have shown that the adaptive response is induced by chronic g-irradiation (dose rate: 1 mGy/min) with the priming exposure dose from 100 mGy to 2500 mGy in mouse m5S cells, and that an isoform of protein kinase C (PKC), PKCa, is essential for the induction of radioadaptive response. Here, we investigated whether p38 MAP kinase a (p38a), another protein kinase that is an important player in cellular signal transduction, is involved in radioadaptive response induced by chronic g-irradiation. Our data indicates that p38α plays an important role in the induction of radioadaptive response.

iii) Analysis of the molecular mechanism of tritium radiation-induced DNA damage response

As genomic DNA forms stable chromatin structure with histone proteins, this stable structure has to be remodeled with histone modifications in response to generation of DNA damage to repair damaged DNA. However, the role has been unclear in cellular responses to low dose rate irradiation. In our study, we found that several histone modifications were accumulated around DSB damage.

Publication list

1) Sasatani, M, et al. *PLoS One.* 10(2) e0117845 (2015)
2) Shimura, T, et al. *Radiother. Oncol*. 112(2): 302, (2015)