§22. 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

・Reactive oxygen species (ROS) increase at low dose rate irradiation

Exposure to ionizing radiation induces DNA double-strand breaks (DSBs) in genomic DNA, while it also causes increases in endogenous ROS. However, the biological effects of such ROS increase, particularly under low dose (rate) irradiation, have been unclear. We first found that low dose rate irradiation increased endogenous ROS in normal human fibroblasts and this increase was sustained after the end of irradiation, but not in cancer cell lines. Such ROS increase caused the arrest in G1/G0 phase. Furthermore, low dose rate irradiation also increased mitochondria mass only in human fibroblast. Thus, low dose rate irradiation might cause sustained ROS increases through the effect to mitochondria.

・The role of mitochondria on damage responses at low doses of ionizing radiation.

The effects of ionizing radiation (IR) have been well investigated using acute single radiation at high doses. DSBs in the cell nucleus produced by IR are considered to trigger genomic instability, a hallmark of cancer in irradiated cells. Although health risks associated with low-dose radiation are currently being investigated intensively, the effects of low-dose radiation remain unclear owing to a lack of sufficient studies. We investigated the cellular response of normal human fibroblasts to repeated exposure to low-dose radiation. In contrast to acute single radiation, low-dose fractionated radiation (FR) with 0.01 Gy/fraction or 0.05 Gy/fraction for 31 days increased in mitochondrial mass, decreased cellular levels of the antioxidant glutathione and caused persistent accumulation of mitochondrial ROS. Excess mitochondrial ROS perturb AKT/cyclin D1 cell cycle signaling via oxidative inactivation of protein phosphatase 2A after low-dose long-term FR. The resulting abnormal nuclear retention of cyclin D1 induces genomic instability in low-dose irradiated cells. In conclusion, we revealed the link between mitochondrial ROS and cell cycle perturbation associated with the genomic instability of low-dose irradiated cells. This study suggests that mitochondria are as target organelles for low-dose radiation.

Publication list

1) Saito Y, et al. *Genes Genet Syst* 90(4) 195-208, 2015
2) Shimura T, et al. *Oncotarget* 7(3) 3559-70 *in press*
3) Shimura T, et al. *Cell cycle* 15(8): 1099-107 *in press*