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Tritium biology in Japan: A search for a new approach

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ABSTRACT

The health effects of tritium are a major public concern in Japan due to the presence of tritium (HTO) contaminated water at the Fukushima Dai-ichi Nuclear Power Plant (Fukushima NPP). From a scientific view, the biological effects of the contaminant HTO at the Fukushima NPP could conceivably be quite small, but the possibility of stochastic effects from tritium radiation cannot be neglected. This reasoning is based on the linear no-threshold (LNT) model, which is cited in ICRP recommendations and suggests an elevation in the frequency of the stochastic effects of radiation, even when the doses are less than 100 mGy. However, at the present, only a small amount of experimental data is available describing the biological effects of low doses radiation, and there are no established experimental systems that can clearly show whether or not the LNT model is appropriate. This is due to a wide scatter in data for the incidence of stochastic effects, which makes it difficult to distinguish radiation-induced events from spontaneous events. We propose overcoming this difficulty for radiobiology experiments using low doses or low dose rate radiation by establishing hypersensitive assay systems, and report on the current status of work investigating tritium radiobiology in Japan.

1. Introduction

A major target of ionizing radiation in the cells of living organisms is thought to be DNA. Low LET (linear energy transfer) radiation, such as gamma-rays or low energy beta-rays, induces DNA damage through direct ionization and through indirect reactions via the generation of reactive oxygen radicals such as hydroxy-radicals. Cells possess the ability to repair such DNA damage through reactions that depend on repair factors or repair enzymes. When damage is not properly repaired, it can lead to the mutation of genes or induce cell killing. The induction of cell killing due to a significant dose of radiation in a short period can result in dysfunction in tissues or organs such as a reduction in the number of blood cells, loss of hair, infertility, or individual death. In contrast, when damaged cells are still alive after an exposure but contain some genetic alterations, these cells may have a potential to transform into cancer cells after several years or decades (Fig. 1) [1].

From clinical studies, the biological effects of radiation can be classified into two types: stochastic effects and deterministic effects. Deterministic effects such as cataracts or loss of hair appear when the exposure dose exceeds a threshold value [1]. Therefore, one can easily predict whether or not the effects may appear if the exposure doses are clear. When the exposure dose is below the threshold for a deterministic effect, such effects will not appear. In contrast to this, stochastic effects, which involve cancer induction and genetic alterations such as somatic mutations, are thought to have no threshold dose and the incidence is in proportion to the radiation dose. Thus, stochastic effects conceivably can appear, even when radiation doses are quite low, although the rate of occurrence of incidents resulting from low dose exposures should be quite low.

Although epidemiological studies provide evidence for increased cancer risks for doses above 100 mSv [2–4], excess cancer risks resulting from doses of less than 100 mSv cannot be observed. Although there are several hypotheses concerning the stochastic effects of low dose exposures, none of them are widely accepted. This is the reason why international and domestic regulatory organizations involved in radiation protection recommend the use of the so-called 'linear no-threshold' (LNT) model, in which cancer risks from low doses (100 mSv) are extrapolated from risks generated by moderate to high doses by hypothesizing a linear dose-response relationship [5,6] (Fig. 2)

Presently in Japan, tritium contamination is a major public concern because the volume of contaminated water is still increasing at the Fukushima Dai-ichi Nuclear Power Plant (termed the "Fukushima

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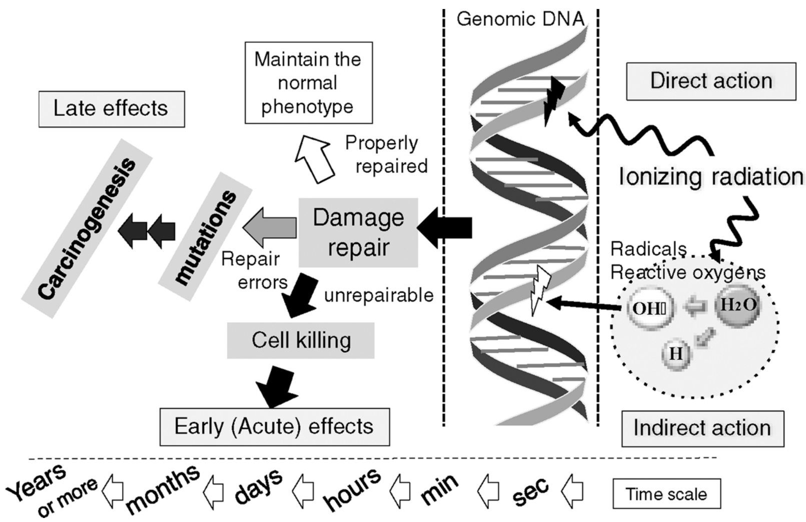

Fig. 1. Time course and events in irradiated biological organisms. The target of radiation is thought to be DNA. DNA is damaged by direct action or indirect action. A majority of the DNA damage is repaired within several hours. If some lesions are not properly repaired, cell killing or carcinogenic changes can result. A large degree of cell killing is a major cause of deterministic effects, and genetic mutations can be a cause of stochastic effects.

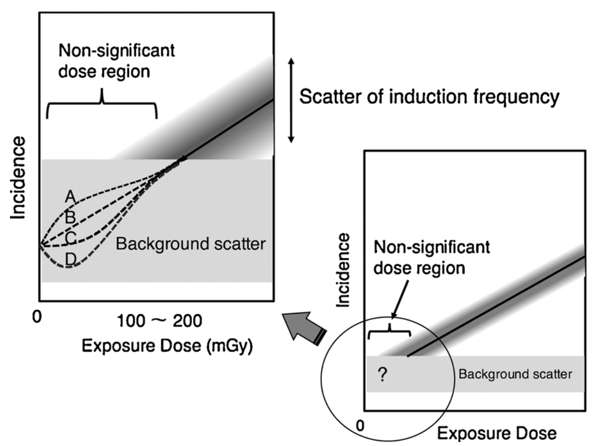

Fig. 2. Dose dependence of stochastic effects. The incidence of stochastic effects show a wide scatter, and the frequency of radiation-induced phenomena also show a scatter. This makes it difficult to distinguish radiation-induced events from spontaneous events in the low dose region below 100 or 200 mGy. Based on experimental observations, there are several hypotheses concerning the dose response for the induction of any stochastic effects. A: enhancement in the low dose region (includes bystander effects), B: linear no-threshold model, C: threshold model, D: radiation hormesis model (partially incorporates the adaptive response).

NPP") as a consequence of the great tsunami which resulted in a severe nuclear power plant accident. Although the majority of radioisotopes in the contaminated water at the Fukushima NPP can be decontaminated by the Multi-nuclide Removal Facility or "ALPS (Advanced Liquid Processing System)", tritium (HTO) still remains in the water, and this prevents the discharge of ALPS-treated water. The total volume of the stored HTO-contaminated water at the Fukushima NPP site is expected to reach 1,000,000 m^3 and the concentration of tritium is 0.5–5 kBq/mL depending the time the water was collected [7]. From a scientific perspective, the biological effects of discharging the contaminated HTO water into the environment could be quite small. However, we cannot neglect the possibility of an increasing number of stochastic effects occurring, when one evaluates the effects using the LNT model. Thus, the LNT model suggests that ionizing radiation always causes detrimental effects, or in other words, an elevation of the incidence of stochastic effects must occur, even when the exposure doses are less than several-tens of mSv.

There are several hypotheses concerning the relationship of the dose to stochastic effects. As mentioned above, the most cited hypothesis is the LNT model that estimates a dose response at low doses by extrapolating the available data from higher doses. There are also three reported radiation associated phenomena in addition to the LNT model: the hormesis model; the threshold model; and the enhanced or bystander model (Fig. 2). However, the understanding of these phenomena is limited to observations in specific experimental systems [8].

At present, only a small amount of experimental data is available describing the biological effects of low doses or of low dose rate radiation, and most of the data is focused on the amount of unrepaired DNA damage [9,10]. In addition, there are no good experimental systems that can clearly show which model is appropriate for risk assessments of stochastic effects. This is due to a wide scatter in the incidence of stochastic effects which makes it difficult to distinguish radiation-induced events from spontaneous or stochastic events. We have been trying to overcome this difficulty in radiobiology experiments using low doses or low dose rate radiation by establishing hypersensitive assay systems [11] or by improving current experimental approaches such as the use of $Apc^{Min/+}$ mouse and *Pig-a* assay. We have also been trying to investigate cellular responses to low doses or to low dose rate exposures at the molecular level. In addition, Japan has one of the largest research communities in the world involved in studies of tritium biology, although the total number of researchers is still small. Here, we describe the current status in Japan of radiobiology work which focuses on tritium.

2. Establishing a hypersensitive system for assessing the biological effects of HTO

A collaborative research group for tritium biology was organized and is supported by the National Institute for Fusion Science (NIFS) at Toki-City, Japan. The group consists of 10 researchers in biology or biomedical departments in 8 institutions. The research areas of the group members are radiation biology, biochemistry, and bioinformatics (Table 1). In the past decade, this group also committed itself to establishing several experimental systems that could be used to detect biological effects from low dose radiation by using laboratory animals or cultured mammalian cells. Our concept for a hypersensitive system is shown in Fig. 3. Because it is difficult to suppress the scatter in the rate of background incidents or events, our hypersensitive system is designed to enhance the appearance of radiation-induced events by subtracting or removing several steps in the pathways leading to carcinogenesis, or by introducing genetic instability by using the techniques from molecular biology or cell engineering.

Using these hypersensitive systems, we have been attempting to determine whether or not any stochastic effects appear after low doses or low dose rate exposures to tritum (HTO) radiation. These projects are still underway, and some of them are described here.