SCIENTIFIC RISK ESTIMATION OF THE HEALTH EFFECTS OF LOW DOSE AND LOW DOSE-RATE RADIATION – AN OVERVIEW

***Tetsuya Ono*[*1] *and Dmytro Grodzinsky*[2]**

[*1]*Dept of Cell Biology, Tohoku University Graduate School of Medicine, 980-8575 Sendai, Japan*
Email: tono@mail.tains.tohoku.ac.jp
[2]*Institute of Cell Biology and Genetic Engineering, 148 Zabolotnogo St., 03143 Kiev, Ukraine*
Email: dmgrod@ukrpack.net

ABSTRACT

Estimation of the scientific risks of high dose radiation has been successfully quantified by many studies using several different approaches. However, the risk for low and low dose-rate radiation is obscure because of a lack of evidence. This risk is currently estimated by extrapolating the radiation response at high doses into low dose ranges for practical purposes. Recent challenges to examine directly the biological responses to low dose radiation using newly developed technologies are unveiling interesting alterations at the molecular level. The interpretation of these data, however, needs careful consideration because they may not be related to any change in biological functions.

Keywords: Low dose, Low dose-rate, Radiation, Biological response, Risk estimation

1 INTRODUCTION

We are surrounded with natural and man-made ionizing radiation and know at the same time that this radiation elicits health hazards at least when the dose of radiation is high. Figure 1 roughly depicts the relationship between radiation dose and health effects together with the radiation levels we face in real life. Thanks to studies in the last 100 years, we now understand quantitatively the risk of radiation, especially when the dose is high. However, the risk of low dose or low dose-rate radiation is obscure because scientific evidence is quite limited.

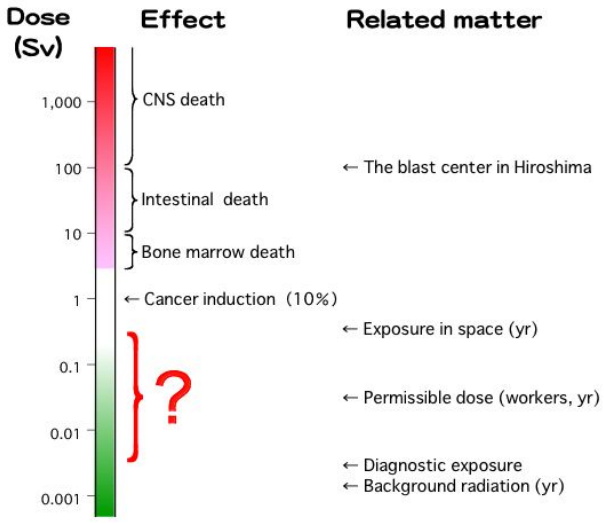

Figure 1. The relationship between radiation dose and health effects. Radiation levels in real life are also indicated. CNS means central nervous system. The question mark shows that the health effects of low dose radiation are not well understood.

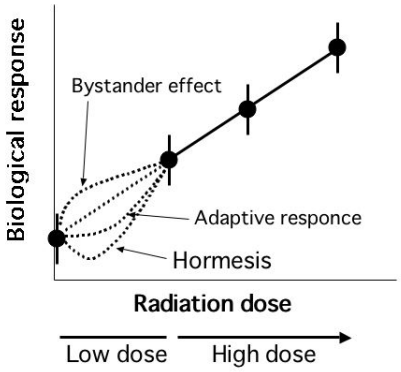

Figure 2. Biological responses to high dose and low dose radiation. At low doses, the dose-response could not be extrapolated from the responses observed at high dose ranges because biological systems respond to low dose radiation in unique ways. The known responses are bystander effect, adaptive response, and hormesis.

Extrapolation of risks at high doses to low doses is not adequate in biological systems because the response to low dose radiation is different from that to high dose. It is now known that creatures recognize low dose radiation as a kind of stress that changes their characteristics in different ways and eventually alters their radiosensitivity. This change is called adaptive response or hormesis. Further, irradiated cells produce some chemicals that influence neighboring non-irradiated cells, a phenomenon called bystander effect. Biological responses to low dose radiation are complicated by another factor called dose-rate effect. These responses are unique to low dose radiation and make it difficult to estimate dose response by extrapolation from the responses to high dose radiation effects (Figure 2). Thus, it is of vital importance to collect evidence on biological responses to low dose radiation (Brenner et al., 2003; Ono, 2007).

Most biological indices show reduced radiation effects if the dose is delivered at a low dose-rate or in a protracted way. This is assumed to be a reflection of the limit of cellular capacity to repair radiation damage. Many radiation-induced lesions cannot be repaired if they are produced in a short period of time, such as in the case of acute irradiation, whereas most are repaired if the lesions are delivered at a slow rate, such as in the case of low dose-rate irradiation. Although the precise mechanisms are yet to be solved, the dose rate effect is an important factor in risk estimation of radiation because we can be exposed to both of these irradiation modalities (Sorensen et al., 2000). Above all, the dose-rates of about 20 mGy/yr and 200 mGy/yr are of critical interest because they correspond to the dose limit for radiation workers and the dose level in space stations, respectively (Figure 1). Studies on the biological responses to these very low dose-rates are extremely limited.

For evaluating the risk of low dose-rate irradiation in humans, epidemiological studies on people exposed in the Chernobyl nuclear accident play a pivotal role because most of them were exposed for a long period of time to a very low dose-rate (Ron, 2007). In contrast, the victims of atomic bombs in Hiroshima and Nagasaki were exposed to high dose-rate radiation. Comparative studies of these two populations will provide a clue to understanding dose-rate effects in humans.

In the following sections, we introduce two recent topics on the effects of low dose and low dose-rate irradiation. They provide new views in estimating the risk of low dose radiation.

2 OMICS ANALYSIS

Recent developments in biotechnology have made it possible to analyse a large number of genes and gene products at one time. Applications of this technique are now revealing interesting effects of low dose and low dose-rate radiation (Amundson et al., 2003; Fujimori et al., 2005; Toledo et al., 2006). Very recently, Yin et al. (2009) examined changes in mRNA levels in mouse brains after 0.1 Gy of radiation using a microarray method, which enabled them to analyse about 1,500 kinds of mRNA. Among these, some 400 mRNA revealed more than 1.5-fold changes including both increases and decreases. An analysis of the biological functions of the altered mRNA suggests a similarity to the changes observed in the ageing human brain and also in a brain with Alzheimer's disease. It suggests that a low dose of 0.1 Gy could bring the brain to Alzheimer-like conditions. The biggest problem in interpreting the data was that the change was observed only at four hours after irradiation, and the stability of the change was not examined at all. On the other hand, Nakajima et al. (2008) studied protein levels using two-dimensional gel electrophoresis in livers of mice irradiated for 485 days under very low dose-rates and found that a protein called rhodanese was elevated with a total dose of 414 mGy or 8,000 mGy. Rhodanese is thiosulfate sulfer transferase, which is thought to be involved in the detoxification of cyanide and hydrogen sulfide in mitochondria. Using the same mice, Uehara et al. examined mRNA in their livers and found that several kinds of mRNA involved in lipid and glucose metabolism were altered. The alterations were observed at the three dose-rates examined, 0.042, 0.86 and 16.6 mGy/day (paper in preparation). The lowest dose-rate was similar to that of the dose limit for radiation workers (20 mGy/yr or 0.055 mGy/day). Thus, it is likely that low dose or low dose-rate irradiation disturbs gene expression. The problem recurs if the disturbance continues significantly long enough so that biological functions are affected. The alteration was checked immediately after irradiation but not at other times. It is easy to imagine that the alteration of mRNA or the protein level would not affect biological functioning if it occurs temporarily. The alteration would affect the physiological status of a body only when it lasted for a certain period of time. The three studies mentioned above should be examined once more from a viewpoint of the stability of the altered gene expression.

3 COMPARISON OF CHANGES IN MOLECULE AND PHENOTYPE

It is generally believed that if the quality or quantity of one kind of molecule within a cell changes, cellular phenotypic alteration will result. In particular, a change in the structure of the genome will be accompanied by many phenotypic alterations, such as cellular and organism loss of function, cancer induction, accelerated senescence, etc. However, this idea has been challenged by several recent epidemiological studies on people living in high radiation background areas. Hayata et al. (2004) found an elevated level of chromosomal abnormality in the lymphocytes of residents in the high background area of Guangdong Province of China, where the background radiation level is approximately 3- to 5-fold higher than that in a control area. On the other hand, the studies on cancer incidence and life span for the people living in this area revealed no elevation of cancer incidence or life shortening (Tao et al., 2000;, Sun et al., 2000). A similar observation was reported in the study of residents in another high background area in India (Ram et al., 2009).

These lines of evidence seem to suggest that the alteration in biomolecules is not always associated with a physiological change. In other words, the change in biomolecules may not necessarily be related directly to health effects or risk. The alteration in molecules should always be accompanied with the question, 'Is it related to an alteration in phenotype?' These multifaceted approaches are important in evaluating biological responses to low dose radiation.

4 CONCLUSION

In order to understand the risk of low and low dose-rate radiation, the experimental studies on the biological responses to these types of radiation play important roles. Recent advances in life science research are making it

possible to evaluate subtle and infrequent changes in biomolecules. Furthermore, the application of these new technologies to the study of biological responses to low and low dose-rate radiation is now revealing unexpected and interesting changes in molecules. The biological consequences of these changes should be considered carefully, however, because the changes might be temporary and not affect biological functions after all.

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