Genomic Instability to Risk of Cancer in Normal Human Cells Induced by Low-Dose X-Rays

Non-targeted radiobiological effects, such as genomic instability and the bystander effect, have important implications for estimating the risk of cancer induced by low-dose/low-dose-rate irradiation, especially chronic low-dose electromagnetic radiation from cesium 137 such as caused by the accident at the Fukushima Daiichi Nuclear Power Plants. However, there have been more studies, both quantitative and qualitative, on radiation-induced non-targeted effects using high-LET(linear energy transfer) radiation than those using low-LET electromagnetic radiation. Using highly precise controlled X-ray microbeams produced by synchrotron radiation, we have been examining how genomic instability leads to biological late effects in order to identify the risk of cancer.

A central paradigm in radiobiology, which is the study of the action of ionizing radiation on living things, has been that energy deposition from radiation tracks into a cell and/or water molecules causes either direct ionization or indirect ionization by hydroxyl radicals, eliciting radiobiological effects. This implies that the radiobiological consequences only affect the cells irradiated directly by the radiation and/or water radicals such as H radical, OH radical and e^-_{aq}, and that non-irradiated cells do not contribute to radiobiological effects. This paradigm is one basis for the current system of risk estimation from radiation, and the risk of radiation-induced cancer after high and moderate doses is relatively well known, based on data from detailed epidemiological studies of Japanese atomic bomb survivors in Hiroshima and Nagasaki [1]. However, the current system of risk estimation has recently been challenged by so-called non-targeted effects, such as the bystander effect (Fig. 1). The radiation-induced bystander effect can be explained as the ability of cells affected by some factors to convey manifestations of cellular damage to neighboring cells not directly hit by radiation. There are many reports regarding the bystander effect after exposure to low-fluence a particles from a plutonium-238 source or helium-ion microbeams. However, few studies have examined the gap-junction mediated bystander effect after exposure to comparatively low-LET electromagnetic radiation such as X- or γ-rays.

Radiation-induced genomic instability can be observed in cells in later generations after irradiation (Fig. 2). Compared with the direct effects of radiation, in which the effects are directly induced as a consequence of direct energy deposition in cells, radiation-induced genomic instability may include non-targeted effects, in which radiobiological effects are seen in cells that are not subject to a direct hit by radiation. In such instances, radiation may have hit cells and a response is communicated from direct-hit cells to non-hit cells, eliciting radiobiological effects ("bystander effect"). Such radiation-induced genomic instability may have important implications for risk evaluation of cancer by low-dose/low-dose-rate irradiation from terrestrial radiation, especially chronic low-dose electromagnetic radiation from cesium 137 such as caused by the accident at the Fukushima Daiichi Nuclear Power Plants, to identify the bystander effect induced by comparatively low-LET electromagnetic radiation.

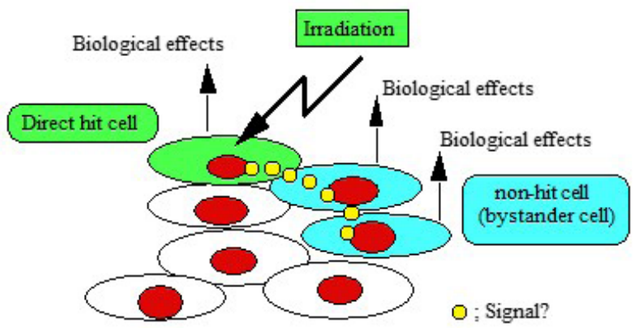

Figure 1: The concept of the radiation-induced bystander effect mediated by cell-cell communication.

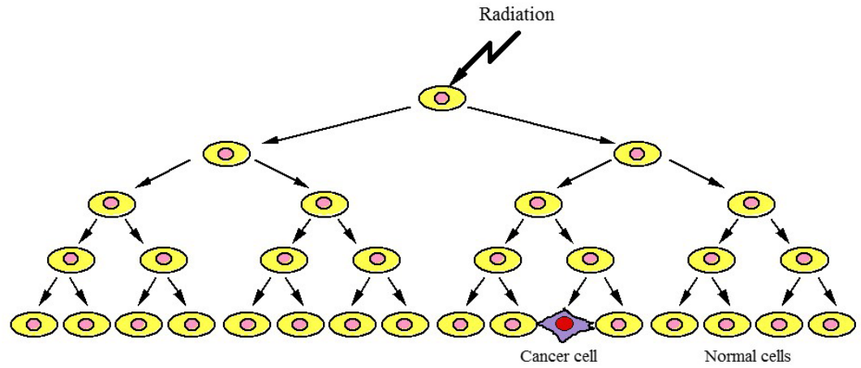

Figure 2: A hypothetical schematic of radiation-induced genomic instability.
A single cell survives after irradiation and is clonally expanded cell generations. During clonal expansion, instability events can occur in the progeny of the irradiated cell.

To identify genomic instability and the bystander effect induced by electromagnetic radiation for estimating risk of cancer, we have been examining gene mutation, as one of the indicators of biological late effects, in normal human cells. A very low number of cells of around 0.04% of the total cell population were irradiated with monochromatic (5.35 keV) X-ray microbeams and the subsequent 20-cell generations were assayed for gene mutation at the hypoxanthine-guanine phosphoribosyl transferase (*HPRT*) locus, which is mapped on the human chromosome X. The mutation frequency of the population was around 50 times higher than that of the non-irradiated control population. When we conducted the same experiment using high-LET carbon-ion microbeams, the mutation frequency was almost the same level as that of the control population. Although acute biological effects caused by comparatively low-LET electromagnetic radiation are less effective than those by high-LET radiation, there is clear evidence that low-LET X-rays can induce late biological effects, such as gene mutation, more frequently than high-LET heavy ions.

To examine the relationship between genomic instability and bystander effect via gap-junction mediated cell-cell communication, we added a specific inhibitor of gap-junction communication (18-α-glycyrrhetinic acid) to the cell population during X-ray-microbeam irradiation. The result showed that the mutation frequency at 20-cell generations after irradiation in the inhibitor-treated cell population was reduced compared to that in the non-treated cell population. The data provides evidence that gap-junction mediated cell-cell communication plays an important role in inducing genomic instability by X-rays. Although no gap-junction mediated bystander effects were observed in acute cellular effects by X-rays using our experimental cell system [2], we conjecture that genomic instability detected with gene mutation occurs in future generations by the bystander effect via gap-junction mediated cell-cell communication as one of the early events immediately after irradiation.

Our study suggests that we must carefully investigate biological late effects and evaluate radiation risks, such as risk of cancer, induced by low-LET electromagnetic radiation such as caused by the accident at the Fukushima Daiichi Nuclear Power Plants.

REFERENCES

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