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## 学位論文内容の要約

### TITLE

Investigation of Cell Responses under Protracted Exposure to Ionizing Radiation

Yusuke Matsuya

### ABSTRACT

Ionizing radiations (particularly X-rays) contribute to not only image diagnosis but also radiation therapy in medical practices, whilst biological effects such as cell kill and mutation after exposure to the ionizing radiations are induced in mammalian cells. Cell kill is one of cell responses caused by some mis-repaired lesions and non-reparable lesions after exposure, which is one of endpoints to discuss non-stochastic effects according to International Commission on Radiological Protection (ICRP). After the accident of Fukushima 1st Nuclear Power Plant (F1-NPP) following the earthquake and tsunami on 11th March, 2011, biological effects (radio-sensitivity) under the protracted (long-term) exposure to low-dose ionizing radiations have drawn a keen interest of the public. Generally interpreted, radio-sensitivity decreases as dose or dose-rate (fluence rate) is decreased. However, recent biological experiments show several reversal radio-sensitivity in low-dose and low-dose-rate range. Evaluation of the reversal radio-sensitivity is a crucial issue from the standpoints of radiation therapy and radiation protection. In this study, focusing on the time course of cell responses during the protracted exposure at various dose-rates, cell responses and radio-sensitivity were investigated by the combination of *in vitro* experimental study and model analysis.

To investigate the time course of cell responses and reversal radio-sensitivity, two main subjects were discussed in this study: one is cell responses and radio-sensitivity under 250 kVp X-rays (standard radiation) protracted exposure at various dose-rates, and the other is development of mathematical modelling considering targeted (energy deposition along radiation particle track) and non-targeted effects (intercellular communication) in wide dose range.

Cell-cycle study showed dose-rate dependence of cell-cycle dynamics in one of the mammalian cell lines, Chinese hamster ovary (CHO-K1), during the exposure at various dose-rates of 0.186-6.0 Gy/h. DNA damage checkpoints through cell cycle depend on the magnitude of dose-rate and the CHO-K1 cells exhibit following cell responses: (i) an cell accumulation in G<sub>2</sub> phase during exposure at lower dose-rates (e.g., 0.186 and 1.0 Gy/h), (ii) the delay of DNA synthesis and an accumulation

of the cells in S/G<sub>2</sub> during the exposure at intermediate dose-rate (e.g., 3.0 Gy/h), and (iii) the blocks of cell cycle progressing in G<sub>1</sub>/M and G<sub>2</sub>/M checkpoints and the delay of DNA synthesis during the exposure at higher dose (e.g., 6.0 Gy/h). The CHO-K1 cells exhibit reversal radio-sensitivity (inverse dose-rate effects: IDREs) with a subtly high radio-sensitivity under exposure at 1.0 Gy/h and an unexpected greater radio-resistance under the exposure at 3.0 Gy/h. The model analysis gives the theoretical explanations that this tendency is caused by the change of DNA amount per nucleus and increases in SLDR (sub-lethal damage repair) rate associated with the fraction of cells in S phase during long-term exposure. Taking account of both the higher radio-sensitivity under 1.0 Gy/h exposure and the radio-resistance after exposure to 3.0 Gy/h, the changes in cell-cycle distribution during exposure might play a key role of modulating the cell survival curve and are possibly responsible for IDREs.

The involvement of intercellular communication between hit cells and non-hit cells (non-targeted effects) in reversal radio-sensitivity was also evaluated. To analyse the mechanism of non-targeted effects, the integrated cell-killing model considering DNA-targeted and non-targeted effects was developed. A couple of new features of this integrated model are given as follows: (i) the traditional stochastic hit theory with linear-quadratic (LQ) relation is adopted to describe the hit probability to emit cell-killing signals, (ii) the repair kinetics of signal-induced DNA lesions is incorporated, and (iii) repair efficiency for lesions induced by intercellular communication is much lower than that in DNA-targeted effects of radiation. Based on this framework, the present model provides quantitative formulae that enable us to describe a series of cell responses such as signal kinetics, DNA repair kinetics and cell survival. The model was verified by comparing with experimental data of signals, DNA damage number per nucleus and cell kill, suggesting that (i) the LQ relation has a potential to express hit mechanism in non-targeted effects and (ii) the low repair efficiency in non-hit cells is intricately related with low-dose hyper radio-sensitivity (HRS). From the model estimation, it was shown that the low-dose HRS is enhanced more as the DNA repair efficiency in non-hit cells is lower, providing new clues to understand the cell responses in non-targeted effects.

In this thesis, the investigations to estimate the contribution of cell-cycle dynamics and low-dose HRS to reversal of radio-sensitivity after long-term exposure are summarised. Through the analysis by the integrated cell-killing model, a couple of new interpretations for cell responses under low-dose or protracted exposure were presented. This study would contribute to more precise understandings of cell responses after the long-term exposure and low-dose exposure to ionizing radiations.