Transactions of the Korean Nuclear Society Autumn Meeting.
Gyeongju, Korea, October 27-28, 2016

Dose rate effect on low-dose hyper-radiosensitivity with cells *in vitro*

Geon-Min Kim* and Eun-Hee Kim
Department of Nuclear Engineering, Seoul National University
1 Gwanak-ro, Gwanak-gu, Seoul, 151-744, Republic of Korea
Corresponding Author: eunhee@snu.ac.kr

1. Introduction

Low-dose hyper-radiosensitivity (HRS) is the phenomenon that mammalian cells exhibit higher sensitivity to radiation at low doses (< 0.5 Gy) than expected by the linear-quadratic model. At doses above 0.5Gy, the cellular response is recovered to the level expected by the linear-quadratic model. This transition is called the increased radio-resistance (IRR). HRS was first verified using Chinese hamster V79 cells *in vitro* by Marples [1] and has been confirmed in studies with other cell lines including human normal and tumor cells.

HRS is known to be induced by inactivation of ataxia telangiectasia-mutated (ATM), which plays a key role in repairing DNA damages [2]. Nakamura et al. [3] observed inactivation in the cells exposed to low dose but only when the dose rate was below certain value. Considering the connection between ATM and HRS, one can infer that dose rate may affect cellular response regarding HRS at low doses. In this study, we quantitated the effect of dose rate on HRS by clonogenic assay with normal and tumor cells.

2. Materials and Methods

2.1 Cell culture and Irradiation

Rat normal diencephalon cells (DI TNC1, CRL-2005, ATCC) and rat gliosarcoma cells (9L/lacZ, CRL-2200, ATCC) were seeded on T-25 flasks. All cells were grown in Dulbecco's modified Eagle's medium (DMEM, Gibco), supplemented with 10% fetal bovine serum (FBS, ATCC), and incubated in a humidified atmosphere of 90 % air and 10% CO_2 at 37 °C.

Cells were irradiated with X-ray beam generated in the YXLON 450-D08 beam tube operating at 150 kV. Dose rates ranged from 0.125 Gy/min, 0.5 Gy/min to 1.5 Gy/min. Dose rate was controlled by changing the beam tube current.

2.2 Clonogenic survival assay

After radiation exposure, cells were incubated for about 10 days. Cells were washed with phosphate buffered saline (PBS, Gibco) and dyed with 5% Giemsa (Sigma Aldich). Colonies were counted as surviving when each of them grows to more than 50 cells.

2.3 Data analysis

The surviving fraction data were fitted to two mathematical models. In the linear-quadratic model

$$S = \exp(-\alpha d - \beta d^2) \cdots (1),$$

α and β are constants and d is the radiation dose. In the induced-repair model [4] which well explains the HRS

$$S = \exp\left\{-\alpha_r\left(1 + \left(\frac{\alpha_s}{\alpha_r} - 1\right)e^{-\frac{d}{d_c}}\right)d - \beta d^2\right\} \cdots (2),$$

α_s is a constant specific to the induced-repair model; α_r is a constant obtained by extrapolating the curve from high dose toward d = 0; and d_c is the "transition" dose from HRS to IRR; β is a constant; and d is the radiation dose. Data analysis was carried out using the OriginLab.

3. Results

3.1 Clonogenic surviving fractions at various dose rates

HRS was observed at 0.125 Gy/min and 0.5 Gy/min of dose rates with both cell lines (Fig 1). Dose rate effect was more obvious with normal diencephalon cells than with gliosarcoma cells. At 1.5 Gy/min, HRS was ambiguous.

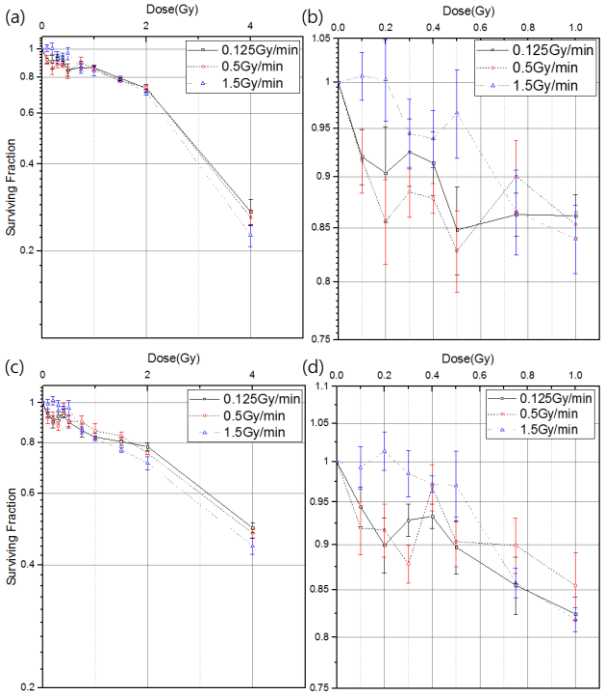

Fig 1. Clonogenic surviving fractions of normal diencephalon cells (a, b) and gliosarcoma cells (c, d) by radiation exposures at various dose rates. The error bars indicate standard errors.

3.2 Data fitting

Data in Fig. 2 were fitted to individual curves. At dose rates of 0.125 Gy/min and 0.5 Gy/min, the induced-repair model better fitted the data than the linear-quadratic model for both cell lines. At a high dose rate of 1.5 Gy/min, induced-repair models were approximated by the corresponding linear-quadratic models.

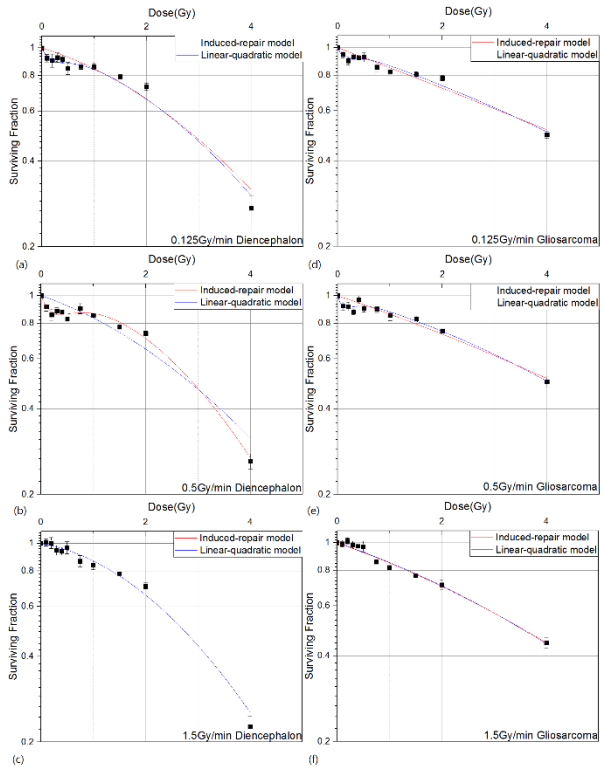

Fig 2. Data fittings to the linear-quadratic and induced-repair models for normal diencephalon cells (a-c) and rat gliosarcoma cells (d-f). The clonogenic surviving fraction data were obtained from exposures at different dose rates for individual total doses.

4. Conclusion

The HRS of cells at low dose exposures is a phenomenon already known. In this study, we observed HRS of rat normal diencephalon cells and rat gliosarcoma cells at doses below 1 Gy. In addition, we found that dose rate mattered. HRS occurred at low doses, but only when total dose was delivered at a rate below certain level.

REFERENCES

[1] B. Marples and M. C. Joiner, The Response of Chinese Hamster V79 Cells to Low Radiation Doses: Evidence of Enhanced Sensitivity of the Whole Cell Population, Radiat. Res., Vol. 133, No. 1, pp. 41-52, 1993.
[2] S. A. Krueger, S. J. Collis, M. C. Joiner, G. D. Wilson and B. Marples, Transition in Survival from Low-Dose Hyper-Radiosensitivity to Increased Radio-resistance is Independent of Activation of ATM SER1981 Activity, Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 4, pp. 1262-71, 2007.
[3] H. Nakamura et al, DNA Repair Defect in AT Cells and Their Hypersensitivity to Low-Dose-Rate Radiation, Radiat. Res., Vol. 165, No. 3, pp.277-82, 2006.
[4] B. Marples and S. J. Collis, Low-Dose Hyper-Radiosensitivity: Past, Present, and Future, Int. J. Radiation Oncology. Biol. Phys., Vol. 70, No. 5, pp.1310-8, 2008.