Quantitative Estimation of Model Parameters for Post-irradiation Recovery of Cells

Jin Kyu Kim [a*], Changhyun Roh [a], Tae Ho Ryu [a], Ludmila N. Komarova[b], Vladislav G. Petin [b]

[a] *Korea Atomic Energy Research Institute, Jeongeup 580-185, Korea*
[b] *Medical Radiological Research Center, Obninsk 209036, Russia*
[*] *Corresponding author: jkkim@kaeri.re.kr*

1. Introduction

It is well known that cell recovery from radiation-induced DNA damage determine the ultimate biological effects produced by ionizing radiation. And thus, the impairment of cell ability to recover from radiation damage would be of great relevance in cancer treatment. It is generally agreed that their efficacy is expressed as a slower recovery rate and a lesser volume of recovery. These effects may be caused by different reasons; the damage of the recovery processes, the increase in the portion of irreversible damage or both of these facts. Therefore, it would be of interest to estimate quantitatively the role of each of those reasons.

The purpose of this study is to suggest a mathematical model pertinent to the post-irradiation recovery and to make an estimation of the model parameters describing post-irradiation recovery of cells exposed to chemicals and ionizing radiation.

2. Quantitative Approach

During the recovery of potentially lethal damage the survival of irradiated cell is increased, i.e. the decrease in the effectiveness of the initial dose D_1 takes place. Then a certain effective dose $D_{eff}(t)$ can be indicated following the recovery during *t* hours. The initial radiation dose D_1 can be considered as being proportional to the mean amount of primary radiation damages, both the potentially lethal (reparable) and lethal (irreversible).

The recovery results in a decrease of the reparable damage. Then the effective dose $D_{eff}(t)$ is proportional to the mean number of residual damages, both the reparable and the irreversible and the ratio

$$K(t) = D_{eff}(t) / D_1 \quad (1)$$

reflects the relative part of the primary radiation damage, which has not been repaired during t hours of recovery. If the ability of cells to recover is saturated or exhausted after sufficiently large time (conditionally $t = \infty$) of recovery, we can write

$$K = K(\infty) = D_{eff}(\infty) / D_1, \quad (2)$$

where $D_{eff}(\infty)$ is proportional to the number of ireversible damage, i.e. the ratio $K(\infty)$ can be considered as an irreversible component.

The decrease in the K(t) with the recovery time *t* can be fitted by an equation of the form:

$$K(t) = K(\infty) + [1 - K(\infty)]\, e^{-\beta t}, \quad (3)$$

where K(t) and $K(\infty)$ are determined by Eqs.1 and 2, respectively; β is the probability of recovery per unit time.
It can be easily shown from here that

$$e^{-\beta t} = [D_{eff}(t) - D_{eff}(\infty)] / [D_1 - D_{eff}(\infty)]. \quad (4)$$

The right part of this equation is the relative part of the radiation damage that the cell is able to recover from, but that has not yet been repaired after *t* hours of recovery. Designating the right part of the Eq. 4 through *A(t)*, we can write

$$\beta = -[\ln A(t)] / t. \quad (5)$$

Thus, knowing the survival and recovery curves after different conditions of treatment with ionizing radiation and different chemical inhibitors of recovery, we can calculate $D_{eff}(t)$ and $D_{eff}(\infty)$. It allows us to draw curves K(t) (Eq. 1) and to calculate the irreversible component K (Eq. 2). Having calculated the dependence of lnA(t) on the recovery time, we can evaluate (Eq. 5) the recovery constant β for various conditions of the combined action.

3. Results and Discussions

Based on the available experimental data on the survival and recovery of the stationary phase cells of Chinese hamster V79 cells irradiated (300 kV X-rays, dose rate being 1.25 Gy/min) and recovered without chemical treatments, estimation of the effective dose was done. Kinetics of the recovery from potentially lethal radiation damage showed that the survival increase due to recovery observed in the controls was gradually reduced as the chemical concentration increased, i.e. the inhibition of the recovery was drug concentration dependent. Using these results, calculation (Eq. 1) was done for the dependency of the relative fraction of the irreversible damage K(t) = Deff(t) / D_1 on the duration of the recovery time of the Chinese hamster V79 cells recovering after irradiation without chemicals and in the presence of various

chemical inhibitors of the cell recovery. It can be noted that the untreated cells subjected to post-irradiation recovery showed an appreciable decrease in K(t) whereas this effect became gradually worse as the chemical concentration increased. It appears that the inhibition of the recovery depends on the drug concentration and is almost complete with 20 mM of pyruvate and lactate and 20 μM of novobiocin and nalidixic acid. For instance, the limited values of K(t), i.e. the values of the irreversible component K = K(∞), are equal to 0.60, 0.75, and 0.92 for the cells recovering from radiation damage without a drug and in the presence of 10 and 20 mM pyruvate, respectively (Fig. 1). Qualitatively similar results could be obtained for other chemicals.

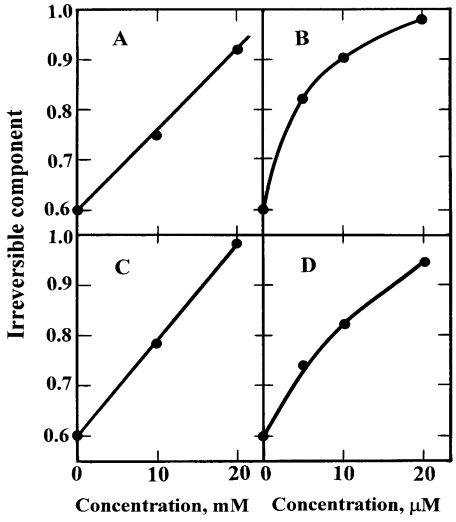

Fig. 1. Irreversible component *K(∞)* of radiation damage in Chinese hamster V79 cells recovering from potentially lethal damage in the presence of various concentrations of chemicals: pyruvate (A), novobiocin (B), lactate (C), and nalidixic acid (D).

It was shown that the basic effect of the chemicals tested at a concentration sufficient to inhibit recovery from potentially lethal damage appears to be a reduction in the number of cells capable of recovery owing to the increase in the irreversibly damaged cells. The findings revealed that (i) the irreversible component of radiation damage was gradually enhanced as the chemicals concentration increased and (ii) the probability of recovery was independent of whether the process of recovery happened with or without chemicals sensitizing the radiation effect. It is not excluded that the first inference may be explained by a conversion by the drugs of radiation induced repairable damage so that the enzymes could then not deal with the lesions.

4. Conclusions

The mathematical approach considered here may be useful to search recovery inhibitors which affect the probability of recovery and the induction of irreversible damage. The radiosensitizing action of various chemical agents was mainly attributable to an increase in the irreversible component of radiation damage. The probability of recovery was in the most cases independent of the treatment conditions. The reduced rate of the recovery process after combined treatments should not be considered as a reason for the synergistic interaction. An overall consideration of these findings is expected to be essential in the design of optimal schedules of combined recovery inhibitors and ionizing radiation treatments in the management of cancer. In addition, the results of this study provide an opportunity for searching agents, selectively or simultaneously acting on the probability of recovery and the yield of irreversible radiation damage.

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