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DNA Repair is Involved in Mechanism of Drug Sensibilization to Ionizing Radiation of Different Quality

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Abstract

It was shown that chemical compounds inhibit the process of cell recovery irradiated with sparsely and densely ionizing radiations. For both types of radiation, it was demonstrated that the irreversible component of radiation damage increases with increasing in drugs concentration, while the recovery constant, characterizing the probability of recovery per unit time, does not depend on the conditions of irradiation. This means that DNA repair is involved in mechanism of drug sensibilisation to ionizing radiation of different quality, which is associated with the formation of additional irreversible damage but not with damage of recovery processes as it was traditionally suggested. The obtained data indicate the prospects of chemical compounds using after irradiation of cells with ionizing radiations of different quality.

Keywords: ionizing radiation, survival, irreversible component, recovery constant, bleocin, doxorubicin, endoxan, fluorourozil, cisplatin.

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1. Introduction

The problem of biological action of high-LET (LET - linear energy transfer) radiation is now very important not only for radiation industry but also for radiation therapy, sterilization, aerospace flights and ecology problems newly arising after Chernobyl and Fukushima reactor accidents. Actually, densely ionizing radiations are responsible for a half of natural radiation dose. Secondly, it is promising to use densely ionizing radiation in the cancer treatment because of high values of the relative biological effectiveness (RBE), as well as due to the suppression of the cell ability to recover from sub-lethal and potentially lethal damage [1]. While considerable knowledge about repair processes in cells exposed to ionizing radiations has been gained during past decades, the situation is far less clear for the combined action of ionizing radiations of different linear energy

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transfer (LET) with medical drugs applied for inhibition of cell ability to recover from radiation damage. It is known that the chemical inhibition of this process is related with inhibition of cell recovery, which is displayed by decreased repair rates at molecular and cellular levels [2]. It may be inferred that the mechanism of cell recovery inhibition by drugs can be attributed to either the damage of the recovery process itself or to the increase in the portion of irreversible damage that could not be repairable at all and reduces or prevents further recovery to occur. In the last case, the process of recovery may be either also damaged or stayed unchanged. However, the data distinguishing these possibilities are lacking in literature. It would be of interest to estimate quantitatively the role each of these possibilities. Although the combination of ionizing radiation with drugs is of considerable current interest, there have been no reports in the literature on a quantitative estimation of each of these reasons after exposure to high-LET radiation. Moreover, there are little comparative investigations of cell recovery inhibition after exposure to low- and high-LET radiation [1, 2].

Thus, the purposes of this study were as follows: (1) to compare the effectiveness of yeast cell recovery inhibition by various medical drugs after cell exposure to radiations with different LET; (2) to evaluate whether the change in the extent and the rate of recovery is preceding through the alteration repairable and irreversible portions of the damage inflicted.

2. Materials and methods

Diploid (strain XS800) yeast cells of *Saccharomyces cerevisiae* was used in our experiments. Cells from the same suspension were exposed to ^{60}Co γ-rays (LET = 0.2 keV/µm, 20 Gy/min) and ^{239}Pu α-particles (25 Gy/min). Yeast cells were chosen as a test object in this study because of some reasons. First, radiobiological responses of yeast cells are qualitatively identical to those of cultured mammalian cells. Second, their recovery has been well studied both on cellular and molecular levels. Furthermore, the ability of eukaryotic cells to recover from radiation damage was first discovered in experiments with yeasts. And at last, a quantitative approach describing the liquid holding recovery (LHR) of yeast cells was successfully applied for combined action of ionizing radiation with various chemical agents on cultured mammalian cells. The γ-ray dose rate was measured with a calibrated Siemens ionization chamber. The LET of α-particles reaching a cell monolayer was estimated to be of 120 keV/μm. Exactly at about this LET value the maximum of RBE-LET relationship was observed for most eukaryotic and some prokaryotic unicellular organisms. Details of these procedures have been described before [2]. Yeast cells are the simplest model of eukaryotes,

radiobiological characteristics of which do not differ qualitatively from response of cultured mammalian cells. Survival response was determined on the basis of the colony counts obtained at the end of 2–3 days of incubation at 30◦C as in the next line. Cell recovery in the post-radiation period occurred in non nutrient condition at 30°C.

Procedure of quantitative estimation of the recovery parameters have been described in detail [2]. The process of LHR may be considered as a reduction of the initial dose D_1 to a certain effective dose $D_{\text{eff}}(t)$ after a recovery during t hours. The decrease in the effective dose $D_{\text{eff}}(t)$ with the recovery time t may be fitted by an equation of the form

$$D_{\text{eff}}(t) = D_1 \left[K + (1 - K) \cdot e^{-\beta \cdot t} \right], \tag{1}$$

where β is the recovery constant that characterizes the probability of the recovery per unit time. The fraction of radiation damage K is an irreversible component of radiation damage, which can be determined as

$$K = D_{\text{eff}}(\infty) \big/ D_1, \tag{2}$$

where $D_{\text{eff}}(\infty)$ is the effective dose corresponding to the plateau of the recovery curve. Then the function

$$K(t) = D_{\text{eff}}(t)/D_1 \tag{3}$$

reflects the relative part of unrepaired damage, both repairable and irreversible, which has not been repaired during t hours. Combining equations (1) and (2), one can deduce

$$A(t) = e^{-\beta \cdot t} = \frac{D_{\text{eff}}(t) - D_{\text{eff}}(\infty)}{D_1 - D_{\text{eff}}(\infty)}. \tag{4}$$

In biological terms, $A(t)$ reflects the relative part of the reparable damage that has not been repaired after t hours of recovery. It follows from this equation that the recovery constant β may be presented as

$$\beta = - \left[\ln A(t) \right] / t \tag{5}$$

Thus, knowing the survival and recovery curves after cell exposure to low- and high-LET radiation, one can calculate the corresponding values of $D_{\text{eff}}(t)$, $D_{\text{eff}}(\infty)$, K, $A(t)$, and β.

3. Results

Figs. 1, 2, 3 exhibit the dependence of cell survival vs. dose of γ- as in Materials and Methods (Panels A) and α as in Materials and Methods irradiation (Panels C) and

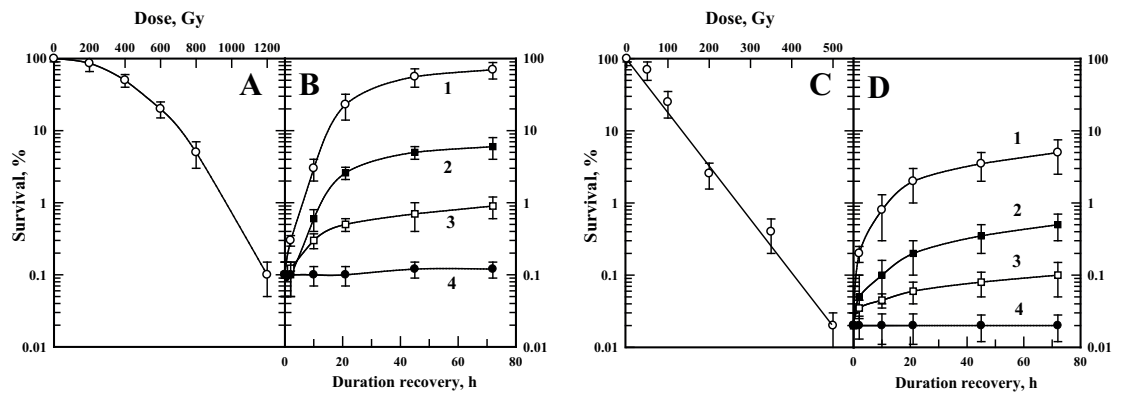the duration of cell recovery after γ- as in Materials and Methods (panels B) and α as in Materials and Methods irradiation (panels D) in the presence and absence of bleocin (Fig. 1), doxorubicin (Fig. 2), and cisplatin (Fig. 3). Analogous outcomes were obtained for endoxan and fluorourocil. Using these results and the above equation, we calculated the parameters characterizing the process of recovery. The final results are summarized in Table. It is obvious that in all cases recovery inhibition was related with an increase in the proportion of irreversible damage (K), while the recovery constant (β as in Materials and Methods) did not depend on the quality of radiation and the presence of drugs explored for inhibition of recovery.
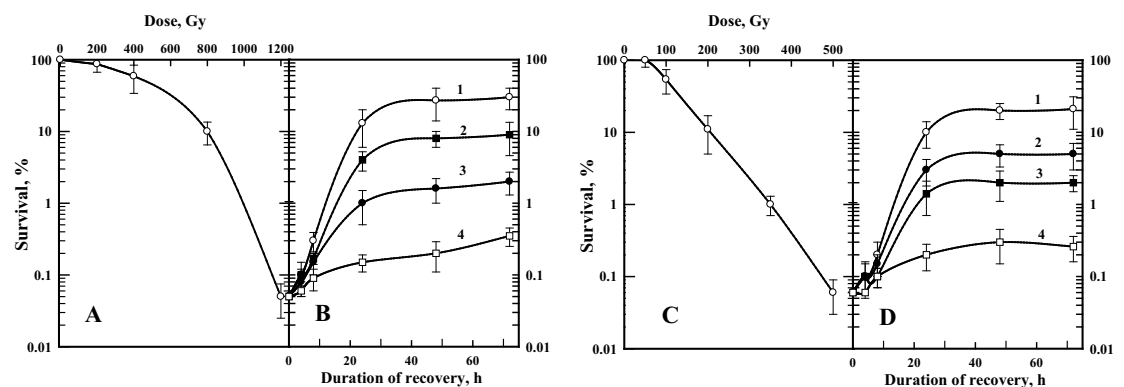
Figure 1: The dependence of *Saccharomyces cerevisiae* cells survival on dose of γ- as in Materials and Methods irradiation (Panel A) and α- as in Materials and Methods particles (Panel C) and the duration of cell recovery after exposure to γ as in Materials and Methods rays (Panel B) and α- as in Materials and Methods particles (Panel D). Cells were recovered in the absence of bleocin (Panels B and D, curves 1) and in the presence of 0.0002 mg/ml (curve 2), 0.0004 mg/ml (curve 3), and 0.002 mg/ml (curve 4) of bleocin.
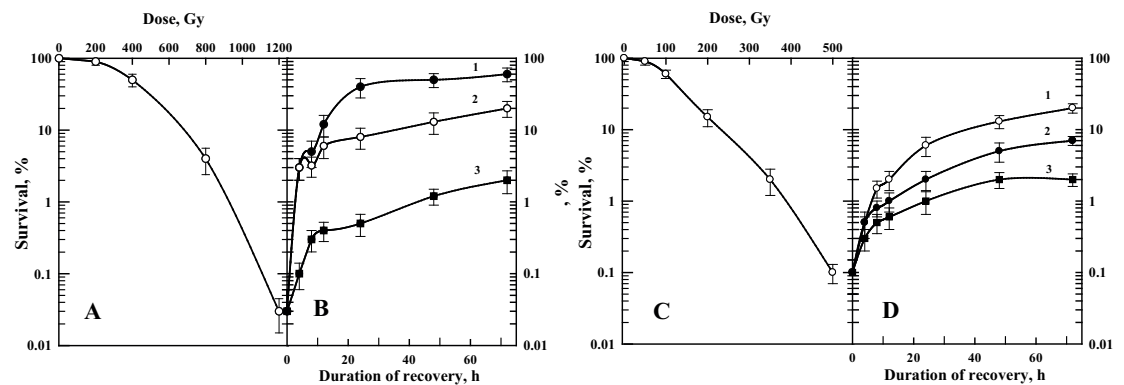
Figure 2: The dependence of *Saccharomyces cerevisiae* cells survival on dose of γ- as in Materials and Methods irradiation (Panel A) and α as in Materials and Methods particles (Panel C) and the duration of cell recovery after exposure to γ- as in Materials and Methods rays (Panel B) and α as in Materials and Methods particles (Panel D). Cells were recovered in the absence of doxorubicin (Panels B and D, curves 1) and in the presence of 0.002 mg/ml (curve 2), and 0.02 mg/ml (curve 3) of doxorubicin.

Figure 3: The dependence of *Saccharomyces cerevisiae* cells survival on dose of γ- as in Materials and Methods irradiation (Panel A) and α as in Materials and Methods particles (Panel C) and the duration of cell recovery after exposure to γ- as in Materials and Methods rays (Panel B) and α as in Materials and Methods particles (Panel D). Cells were recovered in the absence of cisplatin (Panels B and D, curves 1) and in the presence of 0.0002 mg/ml (curve 2), 0.002 mg/ml (curve 3) and 0.02 mg/ml (curve 4) of cisplatin.

TABLE 1: Influence of medicinal drugs of various concentrations on the radiobiological parameters characterizing the process of yeast cell recovery irradiated with γ- as in Materials and Methods rays and α as in Materials and Methods particles.

Drugs (mg/ml)	Irreversible component of radiation damage K		The probability of recovery β as in Materials and Methods, hour^{-1}
	γ- as in Materials and Methods	α as in Materials and Methods	
Without drugs	0.35	0.33	0.07
Bleocin (0.0002)	0.66	0.50	0.07
Bleocin (0.0004)	0.76	0.64	0.07
Bleocin (0.002)	0.88	0.84	0.07
Doxorubicin (0.002)	0.47	0.50	0.07
Doxorubicin (0.02)	0.71	0.70	0.07
Cisplatin (0.0002)	0.66	0.62	0.07
Cisplatin (0.002)	0.80	0.80	0.07
Cisplatin (0.02)	0.98	1.00	0.07
Endoxane (0.002)	–	0.44	0.07
Endoxane (0.2)	–	0.71	0.07
Fluorouracil (0.2)	–	0.50	0.07
Fluorouracil (0.5)	–	0.65	0.07

4. Conclusions

In this paper, the dependence of cell survival on exposure dose and the duration of the LHR have been obtained for diploid yeast cells irradiated with ionizing radiation of different LET and recovering during postirradiation period without and with various concentration of drugs, which widely used in clinical practice as inhibitors of cell recovery. The major point to be inferred from the data described here is that the postirradiation inhibition of cell recovery by drugs investigated may be revealed equally both after action of sparsely and densely ionizing radiation on diploid yeast cells, the simplest model of eukaryotic cells. The probability of cell recovery was shown to be constant for various conditions of recovery after irradiation with ionizing radiation of different LET. The increase in chemical compounds concentration was shown to result in constant increase in the portion of irreversible damage independently of radiation quality. Then one may believe that drugs inhibition of cell recovery after exposure to low- and high-LET radiations may be completely explained by the production of irreversible damage from which cells are incapable to recover. Very similar results were published for cultured mammalian cells irradiated with sparsely ionizing radiation and treated by various chemical compounds before and during postirradiation LHR [1, 2]. On this basis one may conclude that the mechanism of inhibition of cell recovery may be general both for the simplest and the highest eukaryotes.

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