Section 1. Biology

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EVALUATION OF THE CELL CYCLE DURATION OF TUMOUR CELLS UNDER THE CHANGES OF THEIR OXYGENATION DEGREE

Abstract: The work is devoted to mathematical modelling of the known radiobiological effect — "potentially lethal injuries". We evaluated the value of such indicator as the cell cycle duration of tumour cells under repair of DNA double-strand breaks depending on their oxygenation degree.

Keywords: mathematical modelling, potentially lethal injuries, repair of DNA double-strand breaks, cell cycle duration, photon radiation.

Introduction. The urgent character of this research is caused by the necessity for development of correct mathematical model of the known radiobiological effect called "potentially lethal injuries" (PLI) [1]. Theoretical and practical significance of this effect is connected with its contribution to the degree of injuries to the malignant tumour cells, which should be taken into consideration in radiation therapy [2]. The aim of this work was to evaluate the cell cycle duration of tumour cells as the most adequate indicator that reflects the severity of PLI process.

The results of the study. It is assumed in the work that any factor, which slows down the passing of irradiated cells through the cell cycle stages, is associated with the increase in the dimension of repair of the radiation injuries to DNA and this, in turn, increases the probability of survival of cells. The assumption about the universality of the discussed effect allows us to reckon that the well-known phenomenon of increase in the survival of tumour cells, when they are irradiated under hypoxia, is also associated with the phenomenon of potentially lethal injuries (PLI). The above-mentioned suggests that an optimal indicator of the severity of PLI effect is the cell cycle duration (T). Thus, the problem of PLI modelling is reduced to the mathematical model development that allows to estimate the value of the indicator T. In the present paper we studied only effects that result from irradiation of cells by photon radiation (x-ray or gamma).

Initially, the PLI phenomenon was regarded as the increase in the survival of irradiated cells if they were exposed to radiation not in a nutrient medium but in water. Apparently, the most convincing explanation for this effect is the assumption that the lack of nutrients in a cell slows down the passing of cells through the cell cycle stages, and this slowdown leads to the increase in the dimension of repair of double-strand breaks (DSBs) in DNA of irradiated cells. In its

turn, the increase in the dimension of repair leads to the increase in survival of irradiated cells.

If we accept the suggested way of interpretation of PLI phenomenon, we may assume that it has a more universal character. Namely, we may assume that any factors, which slow down the cell cycle, enhance the dimension of DNA repair and increase the survival of cells. To support this hypothesis, we may mention the well-known phenomenon that consists in the fact that in the course of radiation therapy the radio resistance of tumour cells increases with the growth of their hypoxia degree.

These arguments are the basis for the mathematical model development of PLI phenomenon.

First of all, let us decide what indicator will reflect the discussed effect in the most correct way. Considering our assumption that the degree of the cell cycle slowdown determines the survival of irradiated cells, the duration of this cycle can be used as the specified indicator.

Let us suppose that the cell cycle duration is equal to T. Regardless of the hypoxia degree the cell needs a certain amount of oxygen for the cell division. It is clear that the oxygen consumption rate by the cell depends on the concentration of oxygen in the pericellular environment.

The experimentally obtained dependence of the oxygen consumption rate by the cell on the oxygen concentration in the environment is represented in the current work [2]. From this work and also as a result of our earlier studies [3–5] it follows that the diagram of this experimental dependence can be fairly correctly approximated by two linear sections (not taking the area of tissue necrosis into account), besides, one of these sections describes normoxic segment of the diagram of the discussed function, and the other – hypoxic segment.

The hypoxic segment, we are interested in, is mathematically described as follows:

$$v = \frac{v_m c}{c_r}, \qquad (1)$$

where v – the mass rate of oxygen consumption by the cell, v_m – maximum value of the indicator v (in the case of normoxia), c – the oxygen concentration in the environment, $c_г$ – the oxygen concentration value that borders between normoxia and hypoxia.

The complexity of further modelling is determined by the fact that the value v consists of two functionally different components. One of them $(V_ж)$ is the oxygen consumption rate that is spent on the maintenance of cells. This value is constant. Other component $(V_д)$ is the oxygen consumption rate spent on preparation and implementation of the cell division. Exactly this component is important for further modelling.

It is clear that

$$v_д = v - v_ж = \frac{v_m c}{c_r} - v_ж \qquad (2)$$

Hence, at $c = \frac{c_r v_ж}{v_m}$ the value $v_д = 0$ and we may write down

$$v_д = \frac{v_m (c - c_ж)}{c_г} \qquad (3)$$

where $c_ж$ – the oxygen concentration necessary for the maintenance of cells.

Let us suppose that M is the oxygen mass that is required by the cell for preparation and implementation of division. It is clear that

$$M = T \cdot v_д.$$

The sought-for value T may be calculated by the formula

$$T = \frac{M}{v_д} \qquad (4)$$

and then using the above-mentioned approximation it may be transformed as follows:

$$T = \frac{M \cdot c_r}{c - c_ж} \qquad (5)$$

The received formula for evaluation of the cell cycle duration of tumour cell as the index of severity of PLI effect shows the dependence of T on the oxygen concentration in the environment, the border value of oxygen concentration (between normoxia and hypoxemia), the oxygen concentration necessary for maintenance of cells, as well as the oxygen mass required by the cell for preparation and implementation of division.

Conclusions. Any factor, which slows down the passing of irradiated cells through the cell cycle stages, is associated with the increase in the dimension of repair of the radiation injuries to DNA in these cells, which in turn increases the probability of survival of cells. The increase in the survival of tumour cells, when they are irradiated under hypoxic conditions, is also caused by the phenomenon of potentially lethal injuries. The above-mentioned suggests that an optimal indicator of the severity of PLI effect is the cell cycle duration T. Thus, the problem of PLI modelling was reduced to the mathematical model development, which allows to estimate the value of the indicator T.

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