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COMPARATIVE MATHEMATICAL ANALYSIS OF FUNCTIONAL PROPERTIES OF MICE BONE MARROW IN THE PHASE OF RECOVERY OF COLONY-FORMING UNITS NUMBER AFTER SUB-LETHAL AND REPEATED SUB-LETHAL IRRADIATION

Basing on the analysis of experimental data, reported in [N.V. Butomo et al. Radiobiologiya 28 (1988) 39], by applying original mathematical model, earlier and more intensive recovery of the number of colony-forming units of mice bone marrow was shown after repeated sub-lethal irradiation in the dose of 2.75 Gy, comparing to the recovery process of bone marrow colony-forming units after the first sub-lethal irradiation in the dose of 2.75 Gy.

Keywords: ionizing radiation, bone marrow, functional properties, mathematical modeling.

1. Introduction

The effect of increased resistance to the repeated action of ionizing radiation in the specified periods after the previous sub-lethal irradiation is described for mice, rats, pigs, sheep, dogs [1].

Along with that, the reasons for these phenomena did not obtain an acceptable explanation.

In the investigation [2] an attempt has been made to assess the connection between the state of hyper-resistance and the number of colony-forming units (CFU) of bone marrow (BM) in mice femur after the repeated irradiation.

The authors of the investigation [2] note that their experiments allow concluding that the post-irradiation increase in the radioresistance of the mice is revealed set against the number of BM CFU which is not yet totally recovered. Amongst the reasons for the development of this state, the important role belongs to the changes which determine earlier and more intensive recovery of the BM CFU number after its decrease, caused by the repeated irradiation.

The investigation aims to determine and to compare the quantitative characteristics of population functioning of mice BM CFU on the early stages of the recovery of its number after sub-lethal irradiations, which will allow determining the reasons that define earlier and more intensive reconstitution of the BM CFU number after the repeated sub-lethal irradiation.

2. Materials and methods

The task assigned in the present work is solved by means of the original mathematical model concerning the alterations in the number of BM CFU described in works [3, 4], using the experimental results of the work of N. Butomo and M. Kiprianova [2]. The method for spleen CFU assessment in lethally irradiated mice was described by Till, McCulloch [7]. This is a conventional method for the investigation of hematopoietic stem cells under the influence of ionizing radiation, which allows studying their functional activity and radiation sensitivity [8].

N. Butomo and M. Kiprianova performed the investigations using male mice $(CBA\times C57Bl)F_1$ weighing 18 - 22 g. Animals were irradiated on the RUM-17 X-ray unit under the following conditions: voltage 180 kV, current strength 15 mA, filters 0.5 mm Cu + 1 mm Al, half-value layer 1.25 mm Cu. The dose rate was 10.2 mGy/s at a distance of 52 cm from the anode to the center of the body. The radiation dose was 2.75 Gy, which is sub-lethal for $(CBA\times C57Bl)F_1$ mice. In our opinion, it was chosen to obtain the pronounced response to irradiation, but along with that to reach suitable indices of survival rate, especially with due regard to the necessity of repeated irradiation in the same dose.

The mathematical model was developed based on the original scheme of hematopoiesis, introduced by I. L. Chertkov [5, 6].

According to this scheme, hematopoiesis of the living organism through its whole life is supported by deposited in ontogenesis primitive hematopoietic stem cells, which in the postnatal period populate the territories of BM, where they are situated till the moment of mobilization. Primitive stem cells gradually maturate and stepwise, one by one, to supply the population of BM CFU and take part in the process of hematopoiesis.

3. Results

So, according to the works [3, 4], the equation which describes the alterations in the relative number of BM CFU in mice femur in time $N(t)$, is written as

$$\frac{dN(t)}{dt} = \frac{m_0}{\tau_0 C_K} + \lambda N(t), \quad (1)$$

where $N(t) = \frac{M(t)}{C_K}$, $M(t)$ – number of BM CFU in mice femur at the moment t, C_k – number of BM CFU in mice femur in control; $\lambda = \frac{p-d}{\tau}$ – the reproduction rate of BM CFU, p – percent of the cells, which after the division replenish the population of BM CFU in mice femur, $d = 1 - p$ – percent of the cells, which after the division replenish the population of committed hematopoietic progenitors of mice femur BM; τ – average duration of the cell cycle of BM CFU in mice femur; $\frac{m_0}{\tau_0 C_K}$ – relevant incoming rate of BM CFU to mice femur; m_0 – number of sources of BM CFU incoming; τ_0 – the average duration of the time interval, in which CFU come to BM of mice femur.

The solution to Eq. (1) in the intervals of time, in which parameters $\frac{m_0}{\tau_0}$, λ are constant, which characterize the process of population functioning of BM CFU in mice femur, is written as

$$N(t) = \frac{m_0}{\tau_0 C_K(-\lambda)} + e^{\lambda t}\left(N(t_0) - \frac{m_0}{\tau_0 C_K(-\lambda)}\right), \quad (2)$$

where $N(t_0)$ – the relevant number of BM CFU in mice femur at the moment t_0, t_0 – the beginning of observation.

The results concerning the alterations of the relevant number of BM CFU per one femur after acute sub-lethal irradiation in the dose of 2.75 Gy and repeated acute sub-lethal irradiation in the dose of 2.75 Gy in 12 days after the previous irradiation, which are presented in Tables 1 and 2, are obtained from the experimental results of the work [2] taking into account that C_K – number of BM CFU in femur normally equals to 3190 (3190 ± 330).

Table 1. **Parameters of a mathematical model describing the alteration in the relative number of BM CFU in mice femur during four days after the acute irradiation in the dose of 2.75 Gy**

Before irradiation	Days after the first irradiation					
	2 hours	1 day	3 days	5 days	7 days	12 days
Relevant number of BM CFU per femur						
1	0.0564	0.0204	0.0614	0.1549	0.2815	0.6887
Parameters of the mathematical model						
		$\lambda = 0.412$; $\frac{m_0}{\tau_0 C_K} = 0.005$				

Table 2. **Parameters of a mathematical model describing the alteration in the relative number of BM CFU in mice femur during four days after the repeated (in 12 days) acute irradiation in the dose of 2.75 Gy**

Before the repeated irradiation	Days after the repeated irradiation					
12th day	2 hours	1 day	3 days	5 days	7 days	12 days
Relevant number of BM CFU per femur						
0.6887	0.0382	0.0263	0.1094	0.295	0.5107	0.7865
Parameters of the mathematical model						
		$\lambda = 0.402$; $\frac{m_0}{\tau_0 C_K} = 0.016$				

We will illustrate the method for assessment of mathematical model parameters, which describes the increase of the relevant number of BM CFU in femur during the first four days after the acute irradiation in the dose of 2.75 Gy.

From the Eq. (2), which describes the alterations of the relative number of BM CFU in mice femur after the irradiation during the first four days from the beginning of the observation $t_0 = 1$ day, it follows that

$$N(1) - N(3) = (N(1) - S)(1 - e^{2\lambda}), \quad (3)$$

$$N(3) - N(5) = (N(1) - S)(e^{2\lambda} - e^{4\lambda}), \quad (4)$$

where $S = \frac{m_0}{\tau_0 C_K(-\lambda)}$. Taking into account the meanings of $N(1)$, $N(3)$, $N(5)$ from Table 1, we will get $\frac{N(3)-N(5)}{N(1)-N(3)} = e^{2\lambda} \approx 2.280488$. Hence, $\lambda \approx 0.412$.

From the Eq. (4) we obtain that:

$$S = \frac{m_0}{\tau_0 C_K(-\lambda)} = N(1) - \frac{N(3)-N(5)}{e^{2\lambda} - e^{4\lambda}} \approx -0.0116,$$

then $\frac{m_0}{\tau_0 C_K} \approx 0.005$.

Using the Eq. (2) and the results of the experiments presented in Table 2, using the method described above we will calculate the parameters of the mathematical model, which describes the increase of the relevant number of BM CFU in femur during the first four days after the repeated in 12 days acute irradiation in the dose of 2.75 Gy.

4. Discussion

The estimations of the reproduction rate of the femur BM CFU λ represented in Tables 1 and 2 are practically equal during four days after the acute irradiation and in 12 days after repeated acute irradiation.

Along with that, the relevant incoming rate of BM CFU to mice femur $\frac{m_0}{\tau_0 C_K}$ after the repeated acute irradiation in 12 days during the first four days is practically three times higher than the relevant incoming rate of CFU to mice femur BM during four days after the first acute irradiation.

So, the reason which determines earlier and more intensive recovery of BM CFU number after the repeated acute irradiation may be the significant difference between the relative rate of hematopoietic stem cells' transition as a result of the division to the next level of maturation, which is CFU, after the repeated acute irradiation and the first acute irradiation, which may be the evidence of increased radioresistance of the maturating CFU after the repeated acute irradiation.

5. Conclusions

The mathematical model is proposed which describes the recovery of the relative number of mice BM CFU after the irradiation cease.

Using the experimental data of the authors N. Butomo and M. Kiprianova [2] we obtained by applying the mathematical model the determined parameters, which characterize the recovery of the number of mice BM CFU.

Obtained results allow performing the comparative analysis of the parameters characterizing the early stage of the recovery of mice BM CFU number after the sub-lethal and repeated sub-lethal irradiation.

The method for the investigation of the functional properties of mice BM in the process of recovery of BM CFU number after the irradiation is currently proposed. It allows choosing the optimal variant for applying the characteristics of mice BM reaction to the repeated irradiation in the experimental study.

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ПОРІВНЯЛЬНИЙ МАТЕМАТИЧНИЙ АНАЛІЗ ФУНКЦІОНАЛЬНИХ ВЛАСТИВОСТЕЙ КІСТКОВОГО МОЗКУ МИШЕЙ У ФАЗІ ВІДНОВЛЕННЯ ЧИСЕЛЬНОСТІ КОЛОНІЄУТВОРЮЮЧИХ ОДИНИЦЬ ПІСЛЯ СУБЛЕТАЛЬНОГО ТА ПОВТОРНОГО СУБЛЕТАЛЬНОГО ОПРОМІНЕННЯ

За допомогою оригінальної математичної моделі з використанням експериментальних результатів [N.V. Butomo et al. Radiobiologiya 28 (1988) 39] установлено причину, яка визначає більш раннє та більш інтенсивне відновлення чисельності колонієутворюючих одиниць кісткового мозку мишей після повторного сублетального опромінення в дозі 2,75 Гр порівняно з процесом відновлення колонієутворюючих одиниць кісткового мозку після першого сублетального опромінення в дозі 2,75 Гр.

Ключові слова: іонізуюча радіація, кістковий мозок, функціональні властивості, математичне моделювання.

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СРАВНИТЕЛЬНЫЙ МАТЕМАТИЧЕСКИЙ АНАЛИЗ ФУНКЦИОНАЛЬНЫХ СВОЙСТВ КОСТНОГО МОЗГА МЫШЕЙ В ФАЗЕ ВОССТАНОВЛЕНИЯ ЧИСЛЕННОСТИ КОЛОНИЕОБРАЗУЮЩИХ ЕДИНИЦ ПОСЛЕ СУБЛЕТАЛЬНОГО И ПОВТОРНОГО СУБЛЕТАЛЬНОГО ОБЛУЧЕНИЯ

С помощью оригинальной математической модели с использованием экспериментальных результатов [N.V. Butomo et al. Radiobiologiya 28 (1988) 39] установлена причина, которая определяет более раннее и более интенсивное восстановление численности колониеобразующих единиц костного мозга мышей после повторного сублетального облучения в дозе 2,75 Гр по сравнению с процессом восстановления колониеобразующих единиц костного мозга после первого сублетального облучения в дозе 2,75 Гр.

Ключевые слова: ионизирующая радиация, костный мозг, функциональные свойства, математическое моделирование.

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