Mathematical Biosciences 252 (2014) 1–6

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Radiation quality and the shape of dose–effect curves at low doses of ionizing radiation for eukaryotic cells

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ARTICLE INFO

Article history:
Received 8 April 2013
Received in revised form 26 February 2014
Accepted 1 March 2014
Available online 15 March 2014

Keywords:
Mathematical model
Ionizing radiation
Survival curve
Radiation quality
Eukaryotic cells

ABSTRACT

To explain different yeast and mammalian cell response to low and high linear energy transfer (LET) radiation in low dose region, the dependence of fine target structure on the stage of cell growth was supposed. Theoretical consideration based on this suggestion was carried out. Results of calculations are qualitatively in agreement with experimental data under assuming that hit-event for both mammalian and yeast cells is a group of ionizations produced by the same ionizing particle. In the dependence of cell cycle phase, sensitive sites (presumable the vulnerable sections of chromosomes) can be located either in periphery of cell nucleus forming a thin layer inside the nucleus or distributed evenly over the whole nucleus. Such rearrangement of the target results in the alteration of the dependence of both survival curve shape and the relative biological effectiveness values on radiation quality.

1. Introduction

Cell inactivation is the radiation response which is of interest for radiation therapy and sterilization. The use of radiation with high linear energy transfer (LET) for these purposes is based on the higher values of the relative biological effectiveness (RBE) which is defined as the ratio between dose of sparsely ionizing reference radiation (usually X- or γ-rays) and that of the radiation of interest which will give the same biological effect. The problem of the RBE and low dose effect is now very important not only for radiation therapy and sterilization but also for aerospace flights and ecology problems newly arising after the Chernobyl and Fukushima reactor accidents. Variation of the RBE as a function of dose is also a subject of considerable current interest because of the radiation safety and the value of radiation quality factor for natural radon daughter alpha-particles.

Radiobiological responses of simple eukaryote such as yeast cells are qualitatively identical to those of mammalian cells. This is one of the reasons why yeast cells are considered suitable model system for wide radiobiological investigations. Yeast cells as well as mammalian cells reveal an increase of the RBE with LET until it reaches a maximum around 120 keV/μm from where it declines again. To explain a rising RBE with LET, numerous models have been invoked in which multiple ionizations are deposited in the sensitive target(s). The decreasing of the RBE with increasing LET implies that a particle passing through a critical structure will dissipate more energy in this structure than it is required for damage. However, from a survey of published data it seems there appear to be inconsistencies in the findings with regard of radiation quality on the shape of survival curves of yeast and mammalian cells. For mammalian cells, exhibiting sigmoid dose–response curves at low-LET radiation, many authors have shown a purely exponential response after densely ionizing radiations [1–11]. The change from shouldered to exponential type of survival curves has been also seen when chlorella cells were irradiated with high-LET radiation [12]. It means that the RBE of densely ionizing radiation for such the cases is strongly dependent on the survival level chosen for comparison, RBE being very large (10–15) for low doses approaches ratio of slopes of exponential parts of survival curves (3–5) as level of the survival fraction decreases. Conversely, for diploid yeast cells which have a double set of chromosomes like mammalian cells the shape of survival curves is sigmoid independently of radiation quality [13–27]. We have quoted here a lot works performed with yeast and mammalian cells irradiated with low- and high-LET radiation to emphasize that the observed differences in the responses of these cells are not random and systematically obtained by different researchers. Thus, there appear to be a considerable uncertainty in the findings with regard to the LET dependence on survival curve shape for mammalian and yeast cells at the low dose of ionizing radiation. It must be concluded, therefore, that theoretical model for RBE effects based on the changes in the shapes of survival curves, when radiation quality changes, are not sufficient general to be applicable to various biological objects.

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http://dx.doi.org/10.1016/j.mbs.2014.03.004
0025-5564/

When we take up this problem we are immediately confronted with some awkward questions. Why the RBE of densely ionizing particles is increasing with dose decreasing for cultured mammalian cells and is independent on dose for yeast cells? In other words, why radiation response to low dose of high-LET radiation is qualitatively different for yeast and mammalian cells?

The purpose of this report is to provide an appropriate explanation of the observed distinction in radiation response of yeast and mammalian cells to low- and high-LET. To answer the foregoing questions, we shall consider a possible dependence of internal structure of complex target consisting of genes and chromosomes on the stage of cell growth. Target theory was the first theoretical model that explained an intriguing paradox of ionizing radiation action – a negligible total energy absorbed resulted in a significant damage effect. And although after the target theory other mathematical models were developed, which took into account many of the newly discovered cell responses to radiation, they actually took into consideration the main idea of the target theory – the existence of unique radiosensitive cell micro volumes.

2. Theoretical consideration

2.1. Interpretation of mammalian cell data

As far back as 1958, Howard-Flanders had shown in his "track segment theory" [28] that for objects with exponential survival curves the increase of the RBE with LET increasing may be explained by a simple one-hit model if hit-event is several "ionizations" produced simultaneously by a single particle within the sensitive target. It is reasonable to suggest such a kind of hit-event for both diploid yeast and mammalian cells to explain the similar RBE-LET dependence. The change of the survival curve shape from sigmoid into exponential with increasing LET may be explained by the following suggestions. Cell sensitive volume may be presented as a certain region filled by sensitive sites. The number of sites is very large and every high-LET particle hitting this region can cross many such sites. The site may be damaged only by several ionizations produced by the same particle (dimensions of the site are very small and the probability that two independent particles hit the site simultaneously is negligible). The cell is inactivated when the number of damaged sites reaches a critical value. According to current knowledge, one would expect this region to be identical with vulnerable sections of chromosomes which are crossed by ionizing particles. It is obviously that every chromosome consists of a large number of sections; therefore cell nucleus can contain a lot of sensitive sites even if the number of chromosomes is limited.

This idea may be proved with simple calculations. A complete mathematical description of physical stochastic must yield the probability of incidence of each pattern of ionizations, which depends on radiation quality. For the simplest quantitative analysis of this problem we do not need consider all details of interaction of ionizing particles with a matter, in particular, we may do not take into account the distribution of energy (or a number of ion pairs) in the primary events of interaction (primary ionizations). Most dose–effect curves in radiobiology are consistent with the idea that biological effect results from essentially random transfer of energy from the ionizing particle to critical target structures. Without going into details, we use a number of primary ionizations as a measure of site damage and take into consideration only the facts that a number of primary ionizations per part of particle track and a number of particles per unit of area subjected to random statistical fluctuation and can be described by Poisson distribution.

If LET (L) is the overall number of primary ionizations per unit length of track and t is the thickness of a sensitive site, then the mean number of primary ionizations produced by a particle inside the sensitive site is $a = Lt$. Note that the values of L vary from a minimum of 0.2 keV/μm for the most low-LET radiation (e.g. ^{60}Co) to an optimal value of 120–130 keV/μm, providing maximum biological effectiveness of high-LET radiation (e.g. α-particles of ^{239}Pu).

If the site needs μ primary ionizations to be damaged, then the probability to damage the site is given by

$$\varphi = \sum_{n=\mu}^{\infty} e^{-a} a^n / n! = 1 - \sum_{n=0}^{\mu-1} e^{-a} a^n / n!, \tag{1}$$

where n is the Poisson variate. If an ionizing particle crosses l such sites, the probability to damage i sites by a single particle traversing is given as follows

$$P_{1,i} = \frac{l!}{i!(1-i)!}\varphi^i(1-\varphi)^{l-1} = \binom{l}{i}\varphi^i(1-\varphi)^{l-i}. \tag{2}$$

Assuming that two ionizing particles transit the sensitive volume, it would be expected that the probability to find a cell with i damages is

$$P_{2,i} = \sum_{n=0}^{i} P_{1,n}\cdot P_{1,i-n} = \sum_{n=0}^{i}\binom{l}{n}\cdot\varphi^n(1-\varphi)^{l-n}\cdot\binom{l}{i-n}\varphi^{i-n}(1-\varphi)^{l-i+n}$$
$$= \varphi^i(1-\varphi)^{2l-i}\cdot\sum_{n=0}^{i}\binom{l}{n}\cdot\binom{l}{i-n} = \binom{2l}{i}\cdot\varphi^i(1-\varphi)^{2l-i}. \tag{3}$$

Correspondingly, if j particles cross the sensitive volume, the following relation must be valid

$$P_{j,i} = \frac{(jl)!}{i!(jl-i)!}\cdot\varphi^i(1-\varphi)^{jl-i}. \tag{4}$$

Let the mean number of particles which hit the sensitive volume after irradiation with dose D is m, i.e. $D \sim am$. Then the probability to find a cell with i damaged sites is given by

$$P_i = \sum_{j=0}^{\infty}\frac{e^{-m}\cdot m^j}{j!}\cdot\frac{(jl)!}{i!(jl-i)!}\cdot\varphi^i(1-\varphi)^{jl-i}. \tag{5}$$

Let cell inactivation needs at least k damaged sites. It leads to a survival relationship

$$S = \sum_{i=0}^{k-1} P_i = \sum_{i=0}^{k-1}\sum_{j=0}^{\infty}\frac{e^{-m}m^j}{j!}\cdot\frac{(jl)!}{i!(jl-i)!}\cdot\varphi^i(1-\varphi)^{jl-i}, \tag{6}$$

where S is the proportion of the cell population surviving a dose D. For two-hit process Eq. (6) may be written as

$$S = \exp[-m\cdot(1-(1-\varphi)^l]\cdot[1+ml\varphi(1-\varphi)^{l-1}]. \tag{7}$$

The calculated two-hit curves for S in dependence of am, which is proportional to irradiation dose are presented in Figs. 1–3 for different values of m, which is proportional to LET. In these figures, the dependence of cell survival on the dose D (panels A) and the number of ionizations inside the sensitive site a (panels B) are presented. As was mentioned above, the dose of ionizing radiation (D) is proportional to LET (L), target thickness (t) and the average number of particles (m) crossing the sensitive volume while the mean number of ionizations a inside the sensitive site is proportional to LET and target thickness. As far as these parameters for specific objects are not precisely known, the dose D and LET (L) of ionizing radiation are presented in relative units in all figures. It is of little importance since the aim of this work was only a qualitative explanation of the survival curve shapes. Values of the critical number of primary ionizations μ needed to cause site damage were chosen to be 1, 2, 3, 4, 5 and 6, $l = 10$. If hit-event is one primary ionization, the calculated