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A novel multitarget model of radiation-induced cell killing based on the Gaussian distribution

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ABSTRACT

The multitarget version of the traditional target theory based on the Poisson distribution is still used to describe the dose-survival curves of cells after ionizing radiation in radiobiology and radiotherapy. However, noting that the usual ionizing radiation damage is the result of two sequential stochastic processes, the probability distribution of the damage number per cell should follow a compound Poisson distribution, like e.g. Neyman's distribution of type A (N. A.). In consideration of that the Gaussian distribution can be considered as the approximation of the N. A. in the case of high flux, a multitarget model based on the Gaussian distribution is proposed to describe the cell inactivation effects in low linear energy transfer (LET) radiation with high dose-rate. Theoretical analysis and experimental data fitting indicate that the present theory is superior to the traditional multitarget model and similar to the Linear - Quadratic (LQ) model in describing the biological effects of low-LET radiation with high dose-rate, and the parameter ratio in the present model can be used as an alternative indicator to reflect the radiation damage and radiosensitivity of the cells.

1. Introduction

Ionizing radiation, as an important environmental factor (Wilson, 2000), has often been described as a double-edged sword for human health: it may produce both beneficial and detrimental effects (Hall, 2000). For example, ionizing radiation can not only destroy the structure of biological macromolecule, inhibit cell division and even induce cancer (Arena et al., 2014), but also stimulate the synthesis of biological macromolecules, accelerate cell division (De Micco et al., 2011), and even control cancer (Joiner, 2016), and so on. Whereas in radiotherapy, radiation-induced cell killing is a crucial endpoint for the therapeutic effect, and therefore the survival fraction is widely considered as a gold standard measurement (Joiner, 2016). In general, the cell killing effects are often interpreted as resulting from many types of damage induced by ionizing radiation in cells, such as damage to DNA, enzymes, or other biomolecules, and leading to cell cycle arrest, mitotic catastrophe, senescence, and even apoptosis, etc. The complex biological mechanisms of radiation-induced cell killing require the corresponding biophysical models, which can be used to explain and predict the survival fraction in clinical applications, and even provide useful information on the radiasensitivity of the cells (Friedland and Kundrát, 2014).

Over the years, a significant amount of radiobiological models, mainly including the targeted effects models, have been developed to explain and predict the universal survival curves (Ballarini, 2010). Currently, the typical targeted effects models include target theory (Alpen, 1998; Lea, 1955), "Linear-Quadratic (LQ) model" (proposed by the theory of dual radiation action (Kellerer and Rossi, 1978) and molecular theory (Chadwick and Leenhouts, 1973)), track structure theory (including the amorphous track structure model (ATSM) (Cucinotta, 1996; Cucinotta et al., 1999; Katz et al., 1971) and the Local Effect Model (LEM) (Elsässer and Scholz, 2007; Elsässer et al., 2008; Scholz and Kraft, 1996; Scholz et al., 1997)), mechanical kinetic models (including the repair-misrepair model (RMR) (Tobias, 1985), lethal-potentially lethal (LPL) (Curtis, 1986), saturable repair models (Sontag, 1990), and two-lesion kinetic model (Stewart, 2001)), etc.

Traditional target theory is the earliest quantitative interpretation model for radiation-induced cell killing, where its multitarget version is still used in radiobiology and radiotherapy (Friedland and Kundrát, 2014). Although the target theory is effective for quantitative interpretation of radiation biological effect to some extent, and the theory itself is also constantly evolving, some of its basic assumptions are still debatable. This theory assumes that the radiation-induced lesion is a random process with the hit probability following Poisson distribution. However, some investigators have critically discussed this assumption (reviewed in (Sachs et al., 1997)). Recently, some studies have also

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revealed that the radiation-induced damage distribution in the cell could not be accurately described by a single Poisson statistics in general (Bodgi et al., 2016; Vassiliev, 2012). However, most targeted effects models, including traditional target theory and molecular theory etc., are based on the assumption that the distribution of radiation damage per cell is described by Poisson statistics. This may be one of the main reasons that lead to the inaccurate description of the radiation induced cell killing effects in the present targeted effects models.

In any of these models, a “hit” is defined as an event in which a particle enters the target or an event in which a particle deposits energy in the target. However, such a definition is almost too broad (Vassiliev, 2012). This definition does not clearly distinguish different events for the ionizing radiation damage, for example a low-LET (linear energy transfer) electron just touching the surface of the target and a high-LET ion traversing the target diametrically. That is, the underlying physically-chemical and especially biological processes in these models have not been addressed in detail (Kundrát et al., 2005). A more special definition of events causing biological damage can be found, e. g. in a classification of initial damage (Goodhead et al., 1993). An implication of such definition is that one needs to distinguish two types of events: energy deposition (particle entering the target) and radiation damage (ionization cluster). Therefore, the probabilistic description of the two-stage processes involved in the above radiobiological mechanism should take into account two kinds of numbers: one is the actual number of primary particles depositing energy to the target, the other is the number of radiation damage produced by each particle entering the target. One case in which a Poisson distribution can be justifiably assumed is when the number of radiation damage per entering particle is one. Such an assumption, however, is rather restrictive.

Based on these considerations, the generalized or compound Poisson models are proposed by means of a two-step stochastic process (Gudowska-Nowak et al., 2000, 2004; Kundrát et al., 2005; Vassiliev, 2012; Virsik and Harder, 1981). And different distribution formulas based on the two-stage stochastic models, such as the Neyman's distribution (Vassiliev, 2012; Virsik and Harder, 1981), Gamma distribution (Gudowska-Nowak et al., 2000), negative binomial distribution (Gudowska-Nowak et al., 2000), and other distribution (Kundrát et al., 2005) have been proposed during recent years. These formulas can be used to fit not only the experimental data of cell survival including the hypersensitivity (Kundrát et al., 2005), but also the frequency of DNA fragments (Gudowska-Nowak et al., 2000), chromosome aberrations (Virsik and Harder, 1981), and premature chromosome condensation (Gudowska-Nowak et al., 2004), etc. However, the complex expressions of these formulas limit their applications in radiotherapy.

Based on the idea of the two-step stochastic process of radiation damage, in this paper, we proposed a novel multitarget model based on the Gaussian distribution, and discussed in particular its applications in describing the biological response to the sparsely ionizing radiation with high-dose-rate mode. The present model was simulated and tested by fitting the representative and widely used experimental datasets reported in publications. In addition, a parameter ratio in this model provides a simple and effective method to estimate the degree of radiation-induced lethal damage and radiosensitivity.

2. Theoretical model

The cell killing effect of ionizing radiation depends on the initial pattern of radiation damage and the subsequent repair processes. According to the mainstream view, the main process to determine initial radiation damage should at least include two basic steps (Kundrát et al., 2005): (1) ionizing particles traverse different biological targets in the nucleus, (2) each such traversal particle can produce a certain sublethal damages (SLDs) in each biological target by direct and/or indirect effects, which is also determined by subsequent repair processes. Both steps can be regarded as independent stochastic events. The inactivation of one target is considered to be a sublethal event, and the accumulation of these SLDs leads to the cell killing once all targets are inactivated.

The number of particles traversing the biological targets in the nuclei of individual cells of irradiated sample per unit time is of stochastic nature. The mainstream view in previous studies is that DNA is the critical and sensitive "effective target" in the cell under radiations. Our previous work also got the same conclusion from the model calculation (Zhao et al., 2015). At present, many experimental studies indicate that chromatin loops have been identified as structural subunits that are termed as DNA giant loops (also called domains) (Johnston et al., 1997, 1998). The terminal ends of such domains are attached to the nuclear matrix or fixed in protein complexes. These domains are the critical targets for induction of SLDs that determine the cellular radiation responses. Therefore, the basic assumption of this study proposed here is that there are N equally sized domains (identical biological targets) within the nucleus.

Because the magnitude of domains is much smaller than those of the cell nucleus, a particle traversal through the single biological target in a cell nucleus can be regarded as a rare event. Thus, the number of traversal particles through the biological target in a given cell nucleus per unit time, say i, can generally be described by a Poisson distribution with an average, say a (particles/cm^2/s) (the average particles entering each biological target), which is the proportional absorbed dose rate (J/kg/min or Gy/min).

In addition, it is assumed that the impact of individual particles can be considered as fully random. Assume that a single energy deposition event can produce k (≥ 0) SLDs with probability $p(k|1)$, then, the probability distribution of the total number of SLDs $p(k)$ can be written as

$$p(k) = \sum_{i=0}^{\infty} e^{-a}\frac{a^i}{i!}p(k|i), \tag{1}$$

where $p(k|i)$ is the probability of k SLDs caused by i traversal particles. Furthermore, we assume that the number of SLDs is an additive quantity. So, the total number of SLDs k, is the sum of SLDs produced by individual traversal particles, i.e., $k_1 + k_2 + \cdots + k_i = k$. It means that this process includes a number of single-track events. According to the magnitude of biological target, it is almost impossible that such a small object in the nucleus is hit twice. That is, each single-track event is independent of the last one. Then $p(k|i)$ can be described by the i-fold convolution ($*i$) of $p(k|1)$,

$$p(k|i) = p(k|1)^{*i}, \tag{2}$$

which can be calculated by

$$p(k|i) = \sum_{k_1+k_2+\cdots+k_i=k} p(k_1|1)\cdot p(k_2|1)\cdots p(k_i|1). \tag{3}$$

The process of ionization clusters has been extensively studied with event-by-event simulations, while, to our knowledge, the properties of this distribution $p(k|1)$ have not been established based on Monte Carlo simulations. The form of the function $p(k|1)$ can be tested experimentally with different LET radiations. According to previous studies (Vassiliev, 2012; Virsik and Harder, 1981), $p(k|1)$ can be theoretically assumed to be Poisson distribution with an average, say b (the average SLDs induced by each entering particle), to get an analytical expression that is mathematically easier to handle and still depicts the main characteristics of radiation induced biological processes. In this way, $p(k|1)$ can be written as

$$p(k|1) = e^{-b}\frac{b^k}{k!}. \tag{4}$$

Substitution of Eq. (4) into Eq. (3) leads to

$$p(k|i) = e^{-bi}\frac{(bi)^k}{k!}, \tag{5}$$