Article ID: 1007－4627(2007)02－0094－04

Theoretical Models of Cell Inactivation by Ionizing Particles*

CAO Tian-guang[1], MA Yun-zhi[2], KONG Fu-quan[1], YANG Ming-jian[1,3], ZHUO Yi-zhong[1]

(1 *China Institute of Atomic Energy, Beijing* 102413, *China*;
2 *Research Center for Tumor Diagnosis and Therapeutical Physics and Key Laboratory of Medical Physics and Engineering, Peking University, Beijing* 100871, *China*;
3 *School of Sciences, Hebei University of Technology, Tianjin* 300130, *China*)

Abstract: The several theoretical models of cell inactivation or cell survival fraction are introduced. Emphasis is placed on a new model——Ionization Ionization Clustering Cluster model. In order to understand some of the mechanisms of DNA damage related to cell killing and their dependence on radiation quality, the yields of single track lethal events are compared with the estimated yields of different classes of complex DNA lesions calculated by a fast Monte Carlo methods.

Key words: cell survival fraction; DNA damage

CLC number: Q61 **Document code**: A

1 Introduction

Ionizing radiation can induce various kinds of biological effect, its relative biological effectiveness (RBE) varies not only with the type of radiation and its energy, but also with the type of biological target and the biological end point concerned. The cell survival curve describes the relationship between the fractional survival of a population of radiated cells and the dose of radiation to which the cells were exposed. The end point for survival in experiments is referred to the ability of a cell to reproduce (reproductive death). It does not describe the continued existence of a single cell. The theoretical models estimating the fraction of surviving cells are of the utmost importance to the application of ionizing radiation in radiotherapy. In the case of hadron radiotherapy the biological effect is not given by applied dose only. For example, their RBE has been shown to vary hugely with kinds and energy or linear engery transfer (LET) of ions. The track structure model can simulate the transport of charged particle in medium and give the spatial distribution of the energy deposit in the scale of nanometer. Considering the stochastic of the energy deposit, a concept of ionization clustering cluster to model the mechanism of lethal damages production is proposed. A way is being tried to find to understand some of the mechanisms of DNA damage related to cell killing and their dependence on radiation quality.

2 Theoretical Models of Cell Inactivation

The target theory is considered to be the first basic theory of radiation biological effect[1,2]. There exists local region or structure called "target" in cell, which is sensitive to radiation. The target being hit by radiation can be induced some damage. Cell survival is linked to the number of the hit targets. If target has one hit, it is single

* **Received date**: 22 Jan. 2007; **Revised date**: 27 Mar. 2007

* **Foundation item**: National Natural Science Foundation of China (10647146, 10435020, 10175095)

Biography: Cao Tian-guang(1972－), male (Han Nationality), He'nan Huixian, associate researcher, working on radiation biophysics theory; E-mail: tgcao@ciae.ac.cn

target single hit theory (STSH model), the cell survival fraction $S(D)$ is

$$S(D)=\exp\left(\frac{-D}{D_0}\right), \tag{1}$$

where D is the absorbed dose, D_0 is the average dose of one hit. In multi-target single hit theory (MTSH model), $S(D)$ is

$$S(D)=1-\left[1-\exp\left(\frac{-D}{D_0}\right)\right]^N, \tag{2}$$

where N is the number of the target.

Although the target theory is supported by lots of experiments, there exist some problems. With STSH model in the semi-logarithmic plot, the survival curve represents a straight line. However, experimentally cell survival curves exhibit "shoulder" shape. With MTSH model there exists zero slope at zero dose which has never been observed in experiments.

The linear-quadratic (LQ) model[3, 4] is being widely used in clinical radiotherapy. In this model DNA is assumed to be the most important and key target for the irradiation. The double strand breaks (DSB) of DNA are considered to be the crucial initial damage responsible for subsequent biological effects. The cell survival fraction is

$$S(D)=\exp\left[-(\alpha D+\beta D^2)\right]. \tag{3}$$

LQ model provides a simple parameterization of cell survival characteristics, which roughly agrees with experimental data.

The generalized linear-quadratic model[5] gives

$$S(D)=\exp\left[-(\alpha(D)D+\beta D^2)\right],$$
$$\alpha(D)=\alpha_r\left[1+\left(\frac{\alpha_s}{\alpha_r}-1\right)\exp\left(\frac{-D}{D_c}\right)\right]. \tag{4}$$

where α_r, α_s, and D_c, together with β, are phenomenological parameters that have to be determined by analyzing experimental data. α_s represents the initial slope in the low-dose region and α_r describes the initial slope of the parabolic approximation to the data in the high-dose region. With all four parameters this model enables one to describe the low-dose hypersensitivity phenomenon.

For photo and electron beams, LQ model is used commonly, as the biological effects of these particles are determined by the dose only. The parameters (α, β) are established for the given tissue, used for beams of various energies. On the contrary, large variations have been observed between the effects irradiating by diverse ions of different LET values.

Local effect model (LEM)[6, 7] describes the differences in cell inactivation by diverse particles related to their track structures. The basic inputs in LEM are: the radial dose profile around the path of the primary particle; the size of the cell nucleus; the photon cell-survival curve.

$$S_{ion}=\exp\left[\int_V\frac{\ln S_x(D(r))}{V}\mathrm{d}^3r\right], \tag{5}$$

where V stands for the average nuclear volume, the ion and photo characteristics are indicated explicitly.

In LEM the essential point is that, the "local dose" is assumed to cause the same local damage to cell nucleus as if the same dose were deposited by photon. The total biological damage is obtained by integrating the local damages over the nucleus and all the tracks. The LEM does not address the problem of DNA damage formation and repair explicitly. The non-linear nature of the biological effects is taken account by referring to photon survival cure only. The assumption of equal effectiveness of photon and ion track represents a certain over-simplification. Consequently, also photon cell survival curve has to be known over a very wide dose range.

The probabilistic two-stage model[8] describes the physical and biological processes involved in the corresponding radiobiological mechanism and established the theoretical framework. The model represent experimental cell survival curves not better than the LQ model, its parameters is more than ten.

3 The Ionization Clustering Cluster Model

The most important theoretical model for physical process radiation damage is track structure model. Track structure can provide the spatial distribution of the energy deposit in the scale of nanometer (dose distribution). The deposition of energy is a stochastic quantum mechanical process and can form such as blob or spur structure[9], Fig. 1 gives the interaction point of 1 keV electron track in water vapor in two dimensions projection. From the point view of track structure the irreparable lesions correspond to clustering clusters. Clustering clusters are defined as the track entity that consists two or more clusters (cluster size$>$3 ionizations, proved to be able to cause a reparable DNA lesion, or DSB) in a small space of 10 nm scale, which is the characteristic scale of nucleosome.

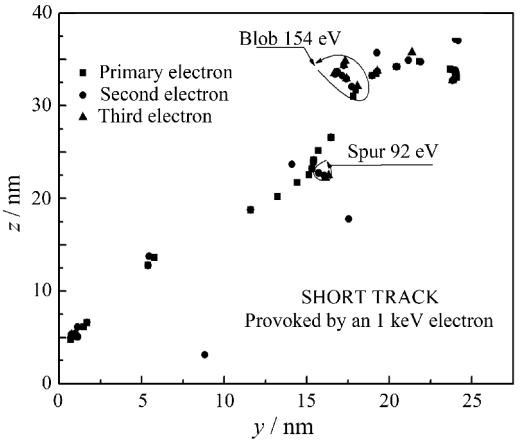

Fig. 1 The interaction point of 1 keV electron track in water vapor in two dimensions.

Motivated by the assumption of interaction of sub-lesions (clusters) in close spatial proximity, on the basis of track structure we have proposed a concept of ionization clustering cluster to model the mechanism of lethal damages production, which is called ICC model. In this model the survival fraction is

$$S(D)=\exp(-\bar{N}_{\text{lethal}}),$$
$$\bar{N}_{\text{lethal}}=(\alpha_1 n_1+\alpha_2 n_2)D+\beta n_1^2 D^2, \qquad (6)$$

where α_1, α_2 and β are biological specific factors. n_1 and n_2 are defined as the average number of track entities that can cause an initial reparable and irreparable damages in a cell nucleus at unit absorbed dose. For deuteron ions at two cell cycle phases the survival curves are calculated and shown in Fig. 2. The results are in good agreement with the experimental data[10].

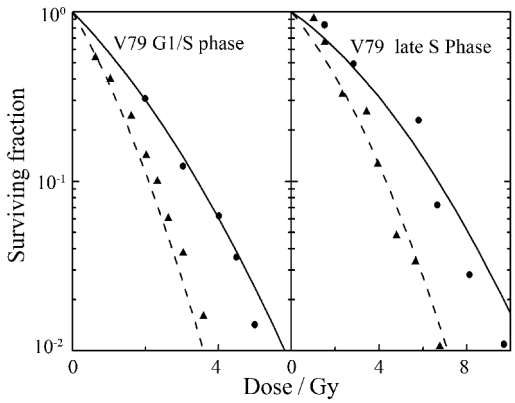

Fig. 2 Calculated survival curves compared with those measured by exposing Chinese hamster V79 cells to mono-LET charged particles.

● Bird et al 20 keV/μm deuteron, ▲ Bird et al 40 keV/μm deuteron, — ICC model 20 keV/μm deuteron, ··· ICC model 40 keV/μm deuteron.

4 Biophysical Interpretation of Lethal DNA Lesions

In order to understand some of the mechanisms of DNA damage related to cell killing and their dependence on radiation quality, we have compared the yields of single track lethal events[11] with the estimated yields of different classes of complex DNA lesions calculated using fast Monte Carlo methods[12]. Fig. 3 gives the initial yields of DSBs, single strand breaks (SSBs), and total lesions with LET of protons with energies from 0.57 to 5.01 MeV. The lethal events are taken from Kundrát result[11]. It shows that the majority of the DNA damage is repaired in a way that is non-lethal.

It is an extremely complex process from radiation induced DNA damage to cell killing. So far,

all the theoretical models are unsatisfactory. More systematic work both on theoretical and experimental sides is needed. It is a big challenge for us to explore and develop the cell damage repair theory based on cellular response to the radiation induced DNA damage.

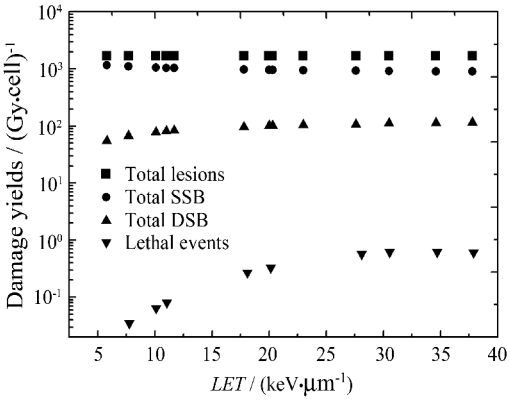

Fig. 3 Initial yield of DSBs, SSBs for protons with energies form 0.57 to 5.01 MeV, yields of lethal events are shown for comparison.

References:

[1] Lea D E. Actions of Radiations on Living Cells. London: Cambridge University Press, 1946, 1—402.

[2] Natarajan A T, Obe G. Mutat Res, 1996, **366**: 65.

[3] Chadwick K H, Leenhouts H P. The Molecular Theory of Radiation Biology. Berlin: Springer-Verlag, 1981, 1.

[4] Sachs R K, Hahnfeld P, Brenner D J. Int J Radiat Biol, 1997, **72**: 351.

[5] Nilsson P, Thames H D, Joiner M C. Int J Radiat Biol, 1990, **57**: 127.

[6] Scholz M, Kraft G. Radiat Prot Dosim, 1994, **52**: 29.

[7] Scholz M, Kellerer A M, Kraft-Weyrather W, *et al*. Radiat Environ Biophys, 1997, **36**: 59.

[8] Kundrát P, Lokajíček M, Hromčíková H. Phys Med Biol, 2005, **50**: 1 433.

[9] Ma Yunzhi, Zhou Hongyu, Zhuo Yizhong. International Journal of Modern Physics, 2005, **B19**: 2 933.

[10] Bird R P, Rohrig N, Colvett R D, *et al*. Radiat Res, 1980, **82**: 277.

[11] Kundrát P, Stewart R D. eprint, http://arxiv.org/abs/physics/0512030.

带电粒子致细胞失活的理论模型*

曹天光[1,1)], 马云志[2], 孔福全[1], 杨明建[1,3], 卓益忠[1]

(1 中国原子能科学研究院, 北京 102413;
2 北京大学医学物理和工程北京市重点实验室, 肿瘤物理诊疗中心, 北京 100871;
3 河北工业大学理学院, 天津 300130)

摘 要: 介绍了经辐射损伤后细胞失活或存活的理论模型及相关问题的一些研究工作。重点考虑了径迹结构和能量沉积特点的新的细胞失活模型。在径迹结构模拟的基础上, 计算并分析了 DNA 损伤谱, 同时把径迹结构得到的损伤谱与细胞存活联系起来, 初步在分子水平上理解了细胞失活或存活的机制。

关键词: 存活率; DNA 损伤

* **收稿日期**: 2007 - 01 - 22; **修改日期**: 2007 - 03 - 27

* **基金项目**: 国家自然基金重点资助项目(10647146, 10435020, 10175095)

1) E-mail: tgcao@ciae.ac.cn