第 22 卷 第 4 期
2005 年 12 月

原子核物理评论
Nuclear Physics Review

Vol. 22, No. 4
Dec., 2005

Article ID: 1007－4627(2005)04－0398－04

Radiation Induced DNA Damage and Related Bio-chemi-physical Problems*

CAO Tian-guang[1], CAI Ming-hui[1,2], GENG Jin-peng[3], KONG Fu-quan[1,2], MA Yun-zhi[4], ZHUO Yi-zhong[1]

(1 *China Institute of Atomic Energy, Beijing* 102413, *China*;
2 *Department of Physics, Hebei University of Technology, Tianjin* 300130, *China*;
3 *School of Physical Science and Engineering, Zhengzhou University, Zhengzhou* 450052, *China*;
4 *School of Physics, Peking University, Beijing* 100871, *China*)

Abstract: Some of recent works are presented on radiation induced DNA damage being carried out at China Institute of Atomic Energy (CIAE) and related bio-chemi-physical problems. Emphasis is placed on track structure and its relation to the cell end-point, and a simple model proposed to study the dynamical behavior of P53-Mdm2 interaction which plays pivotal role in cellular response to DNA damage.

Key words: track structure; survival probability; negative feedback loop

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

1 Introduction

Ionizing radiation to a biological system initiates a highly complex series of physical, chemical, and biological changes that may culminate in cell death, organ dysfunction, or cancer. DNA is assumed to be the most important and key target for the irradiation as it carries message of life. The double strand breaks (DSBs) of DNA are considered to be the most important initial damage responsible for subsequent biological effects. Based on the experimental conditions of HI-13 Tandem Accelerator at CIAE, DSBs of purified DNA in aqueous solution irradiated with heavy ion beams are studied and the DNA fragments are investigated by using atomic force microscopy (AFM)[1-5]. Inspired by the experimental works, a theoretical program accordingly with the goal is carried to understand how the particle transportes in and interactes with the biological system and the biological system responses step by step. Track structure model is based on the event by event Monte Carlo method to simulate the transport of charged particle in medium and give the spatial distribution of the energy deposit in the scale of nanometer and evolution with time in the scale of picosecond. The MOCA-15 code is extended appropriating for low energy electron and the interaction due to the secondary low energy electron (cutoff energy is 1 eV instead of 10 eV in the original code) is considered. A way is being tried to find a bridge between the nascent track structure at physical stage and the biological end point of the cell in various phenomenological ways. DNA damages can perturb the cellular steady-state quasi-equilibrium and activate or amplify certain biochemical pathways. The P53

Received date: 22 Aug. 2005

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

Biography: Cao Tianguang (1972－), male (Han Nationality), Henan Huixian, Associate Researcher, woking on biophysics theory; E-mail: tycao@iris.ciae.ac.cn

tumor-suppressor protein plays a pivotal role in cellular response to DNA damage, for which a simple model is proposed to describe the P53-Mdm2 interaction loop to compare with recent experiments.

2 Track Structure

The effects of high-energy radiation can be perceived as the result of a sequence of events that follow the interaction of the initial particle with media. Primary energy transfer events occur within 10^{-19} s after radiation passes through a cell. Deposition of energy is a stochastic quantum mechanical process, and its spatial distribution is called track structure.

The most important theoretical model for the study of radiation damage is track structure model. So far, track structure model is still at the development stage, within this model media is still treated as water vapor, and the cutoff energy of secondary electron is 10 eV. However, the secondary electrons with energies between 1 and 20 eV are the most abundant ($\sim 5.0\times10^4$ per MeV), and carry most of the energy of the fast initial particle. In present track structure model the interactions due to abundant low energy secondary electrons are neglected. Such electrons, even at energies well below ionization thresholds, can induce substantial yields of single- and double-strand breaks in DNA[6].

We have extended MOCA-15 code developed by Paratzke[7] to include the low energy electron, and have considered the interaction of low energy electron (cutoff energy is 1 eV). Using the code we have simulated the track structure of low energy electrons in water with Monte Carlo method, taking into account inelastic processes such as ionization, excitation, attachment and auto-ionization caused by super-excitation as well as the yield and distribution of some free radicals. By contrasting the characteristics of track structures with 1 and 30 eV as cutoff energy, we have analyzed the role of low energy electrons in track structures. Fig. 1 gives the interaction point of 1 keV electron track in water vapor in two dimensions projection. The electrons of energy above 30 eV make up the shape of track structure with a definite length and width. The electrons of energy bellow 30 eV provide much more dense interaction points and disperse deposited energy[8].

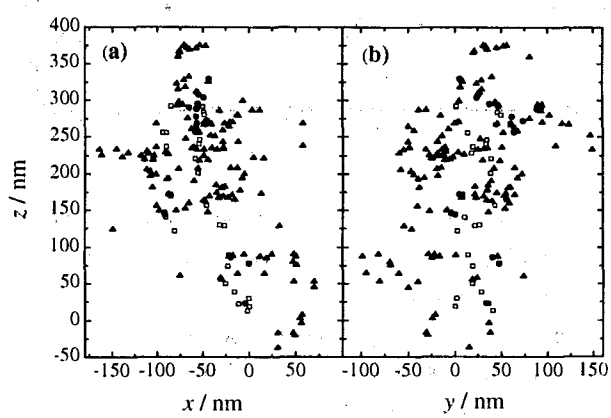

Fig. 1 The interaction point of 1 keV electron track in water vapor in two dimensions.
□ Primary electron, ● Second electron above 30 eV, ▲ Second electron bellow 30 eV.

3 From Track Structure to Biological Effects

It is an extremely complex process for radiation to induce observable biological endpoints. Two main stages can be distinguished for theoretical modeling——molecular damage stage and biological end-point stage.

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. With the help of this concept we are trying to model the production death of Chinese hamster V79 cell at G1/S phase and late-S phase induced by the radiation of proton and alpha particle. The theoretical results are in good agreement with the experimental data of the survival curves[9]. Fig. 2 is the calculated

survival curves compared with those measured by exposing Chinese hamster V79 cells to mono-LET charged particles[10].

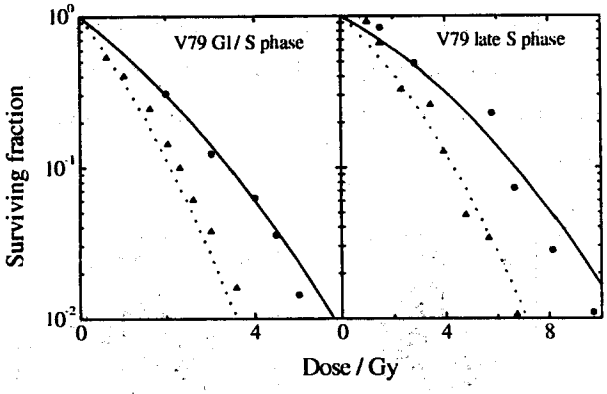

Fig. 2 Calculated survival curves compared with those measured by exposing chinese hamster V79 cells to mono-LET charged particles.

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

The spectra of possible damage configuration produced by ionizing radiation are often obtained from track structure in water combined with geometrical models of DNA. This approach is computationally very expensive and may be impractical for applications. Based on analyzing simulation results[11, 12], four parameters have been used to describe the DNA damage spectra produced by track structure simulations[13]. This algorithm captures the major trends in the DNA damage spectra and is expected to be used as the systematic results applicable to the cases where the detailed simulations are lacking. These spectra can be provided as the input data for the dynamical models to bridge the physical stage and the biological stage.

4 A Simple Model of Cellular Response to DNA Damage

DNA damage is a relatively common event in the life of a cell and may lead to mutation and cellular or organism death if the damage is unrepaired or misrepaired. Damage to DNA induces several cellular responses that enable the cell to eliminate the damage or to activate the apoptosis if the damage is unrepairable. In this complicated network, the P53 tumor-suppressor protein plays a pivotal role. There exists an autoregulatory negative feedback loop between P53 and Mdm2. We have developed a simple model to explain the oscillatory behavior in the activity of these two genes observed in experiments of both population of cells and single cell[14]. Work is in progress[15].

From radiation induced DNA damage to the observable biological end-point is an extremely complex process, which involves many spatial and temporal scales of different orders of magnitude. Link initial molecular damage to higher-level cell and tissue responses through mechanism-based models or other more sophisticated theories is our long-term goal to collaborate with experimentalists.

References:

[1] Sui Li, Mei Junping, Ni Meinan, *et al*. Journal Chinese Electron Microscopy Society, 2003, **22**(2): 87(in Chinese).

[2] Zhao Kui, Wu Xiukun, Guo Jiyu, *et al*. J Chin Electr Microsc Soc, 2003, **22**(3): 219(in Chinese).

[3] Zhao Kui, Wu Xiukun, Guo Jiyu, *et al*. Chin Phys Lett, 2003, **20**(11): 1 947.

[4] Ni Meinan, Zhao Kui, Sui Li, *et al*. Journal of Radiation Research and Radiation Processing, 2004, **22**(2): 106(in Chinese).

[5] 隋 丽, 赵 葵, 倪嵋楠等. 高能物理与核物理, 2004, **28**(10): 1 126.

[6] Badla Boudalffa, Pierre Cloutier, Darel Hunting, *et al*. Science, 2000, **287**: 1 658.

[7] Wilson W E, Paratzke H G. Radiat Res, 1981, **87**: 521.

[8] 马云志, 曹天光, 卓益忠. 高能物理与核物理, 2003, **27**(4): 319.

[9] Ma Yunzhi, Zhou Hongyu, Zhuo Yizhong. Modeling of Radiation Response of V79 Cell Using New Concept of Clustering Clusters. International Journal of Modern Physics B, (to be published).

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

[11] Nikjoo H, O'Neill P, Wilson W E, *et al*. Radiat Res, 2001, **156**: 577.

[12] Nikjoo H, Bolton C E, Watanabe R, *et al*. Radiat Prot Dosim, 2002, **99**: 77.

[13] Cao Tianguang, Ma Yunzhi, Zhuo Yizhong. Research and Simulation of the Spectrum of DNA Damages submitted to ACTA Biophysics SINICA (in Chinese).

[14] Lahav G, *et al*. Nat Genet, 2004, **36**: 147.

[15] Yan Shiwei, Zhuo Yizhong. A Simple Model of Cellular Response to DNA Damage (in preparation).

辐射致 DNA 损伤及相关生物-化学-物理问题*

曹天光[1]，蔡明辉[1,2]，耿金鹏[3]，孔福全[1,2]，马云志[4]，卓益忠[1]

(1 中国原子能科学研究院，北京 102413；
2 河北工业大学物理系，天津 300130；
3 郑州大学物理工程学院，河南 郑州 450052；
4 北京大学物理学院，北京 100871)

摘　要：介绍了在 DNA 辐射损伤以及相关生物、物理、化学问题的一些研究工作。重点是径迹结构、DNA 双链断裂和细胞学终点的关系。P53-Mdm2 负反馈回路在 DNA 损伤的细胞响应方面起重要作用，用一个简单的模型研究了 P53-Mdm2 负反馈回路相互作用的动力学行为。

关 键 词：径迹结构；存活率；负反馈回路

* 基金项目：国家自然科学基金资助项目(10175095)