1st International Workshop on Space Radiation Research and
11th Annual NASA Space Radiation Health Investigators' Workshop
Arona (Italy), May 27-31, 2000

Physica Medica - Vol. XVII, Supplement 1, 2001

Modeling of radiation action based on nanodosimetric event spectra

R. Schulte[1], V. Bashkirov[1], S. Shchemelinin[2], G. Garty[2], R. Chechik[2], A. Breskin[2]

1. *Loma Linda University, Loma Linda, CA 92354 (USA)*
2. *The Weizmann Institute of Science, Rehovot 76100 (Israel)*

Abstract

Assuming that the number of ionizations events within short segments of DNA-size volumes is a major factor of the biological effectiveness of ionizing radiation, we have designed and manufactured a new nanodosimetric detector counting ionization events in small wall-less gas volumes, which simulate such DNA segments. The detector measures individual ionizations in low-pressure (~ 1 Torr) propane or any other gas corresponding to a tissue-equivalent cylindrical volume of 2-4 nm diameter and up to 30 nm length. While first nanodosimetric event spectra with protons and alpha particles are being obtained, it is important to develop and test a theory that relates these spectra to biological endpoints such as strand breakage, mutations, and lethal cellular events. This paper describes the two-compartment theory, which is based on the premise that energy deposition in nanometer sites can be broadly divided into two categories: a low-energy deposition compartment comprising events with a total number of 2-5 ionizations, and a high-energy deposition compartment comprising events containing 6-10 ionizations. Under standard biochemical conditions, these events will lead to different biological consequences. The fate of DNA lesions produced by low-energy deposition events will mostly depend on the repair capacity of the irradiated cells, whereas events produced by high-energy deposition events will be irreparable. These events are therefore the biologically most relevant lesions, since they inevitably lead to mutation and cell death.

KEYWORDS: Nanodosimetry, biophysical model.

1. Introduction

It is generally accepted that for radiation doses larger than a few cGy the DNA is the principal target of radiation action, whereas at lower doses non-targeted effects may supervene [1]. At doses relevant to space travel and radiotherapy, most biological effects occur as a direct consequence of direct DNA damage. In order to understand and model these effects it is important to study how the radiation energy deposited in or near DNA molecules relates to cellular radiation effects.

We recently reported on a nanodosimetric technique that measures ionization events in a wall-less gas volume, which simulates a DNA-equivalent volume [2]. In principle, there are no limitations with respect the working gas, and one may use water vapor or more complex gas mixtures matching the atomic composition of DNA. As new nanodosimetric techniques are emerging, there is a need for nanodosimetric theories of radiation action. Such a theory is presented and discussed in this paper.

2. Concepts of Nanodosimetry

A low-pressure gas model can be used to simulate the stochastic interactions of ionizing charged particles with nanometer spatial resolution. This may be done in two different ways as shown in Figure 1. In the first approach (top of Figure 1), a *single* sensitive site is exposed to a large number of charged particles, and the number of ionizations generated within the site is counted per particle event. In the second approach (bottom of Figure 1), individual track segments are imaged as a whole, and *multiple* randomly oriented sensitive sites are used to sample the track ionizations. Since at present there is no experimental method of track structure imaging with nanometer resolution, this approach is currently limited to simulated charged particle tracks obtained by Monte Carlo simulation [3].

Both approaches can be used as a tool to characterize the biological quality of different forms of radiation based on the stochastic variation of the number of ionizations *j* in individual energy deposition events. Due to the nanometer size of the sensitive site, ionization events for doses less than

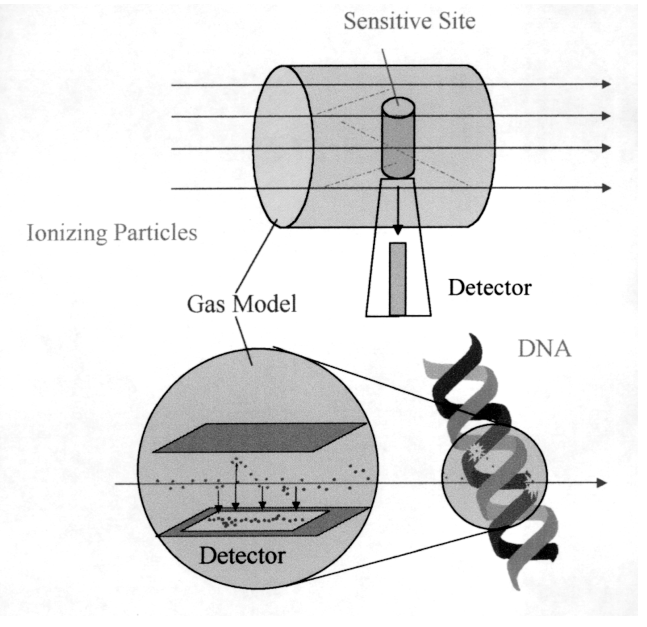

Fig. 1 – Two different approaches to perform nanodosimetry in a low-pressure gas model.

100 Gy are almost always caused by single particles or their associated secondary particles. Therefore, it is possible to normalize event size spectra to unit particle fluence or dose and to scale these spectra to the actual fluence or dose used.

3. Two-Compartment Theory

We propose to use a cylindrical nanodosimetric site of 2 nm diameter, closely matching the size of the DNA double helix, and 16 nm or 50 base pairs length as the sampling volume for ionization event spectra. We assume that *biologically significant damage* consists of *multiply damaged sites* (MDS) or local clusters of DNA damage, which are produced when more than one ionization occurs within such a site. The two-compartment theory assumes two classes of biologically significant DNA damage: reparable damage is caused by 2-5 ionizations within the sensitive site, whereas irreparable damage is caused by 6-10 ionizations. For ionization events with more than 10 ionizations the biological effectiveness is assumed to diminish due to charge and radical recombination events in regions of high ionization density [4, 5].

Reparable damage may either be successfully removed by the intracellular repair system or may lead to permanent damage due to misrepair. It is important to note that all MDS are produced linearly with dose. On the other hand, the induction of lethal damage from *reparable* MDS can be nonlinear with respect to dose. Here we assume that the dose dependence of the induction of lethal damage can be described by a second order (linear-quadratic) polynomial. Due to the absence of repair, the production of lethal damage from *irreparable* MDS is assumed to increase linearly with increasing dose. Furthermore, by assuming a Poisson distribution of lethal damages, the surviving fraction of cells may be expressed as

$$SF = \exp\left[-\left(\alpha_1 q_1 D + \beta q_1^2 D^2\right) - \alpha_2 q_2 D\right] \qquad (1)$$

where D is the absorbed dose, the linear-quadratic term in parentheses corresponds to the induction of lethal damage from reparable MDS, and the linear term, $\alpha_2 q_2 D$, describes the induction of lethal damage from irreparable DNA lesions. The radiation quality factors q_1 and q_2 are defined relative to a low LET reference radiation as

$$q_1 = \frac{\sum_{j=2}^{5} P(j)}{\sum_{j=2}^{5} P_{ref}(j)}, \qquad q_2 = \frac{\sum_{j=6}^{10} P(j)}{\sum_{j=6}^{10} P_{ref}(j)} \qquad (2)$$

where $P(j)$ and $P_{ref}(j)$ are probabilities of finding events with exactly j ionizations per unit dose or particle fluence. The LET dependence of cell survival is uniquely determined by the LET dependence of the quality parameters q_1 and q_2. The cell-specific parameters α_1, α_2, and β are assumed to be independent of LET.

4. Determination of Radiation Quality Parameters

The quality parameters q_1 and q_2 were calculated using published energy deposition probabilities in cylindrical sites of 2 nm diameter and 16 nm length from Monte Carlo-simulated track segments of protons and helium-4 ions in water vapor scaled to unit density [6]. The energy deposition probabilities, which were normalized to a dose of 1 cGy and binned in intervals of 5 eV or 10 eV, were converted to probabilities for the number j of ionizations per event according the following equation:

$$P(j) = \sum_E P(E) P\left(j|E\right) \qquad (3)$$

where $P(j)$ is the probability of events with j ionizations, $P(E)$ is the probability of events falling into the bin centered around the deposited energy E, and $P\left(j|E\right)$ is the conditional probability of producing j ionizations in events belonging to the energy-deposition bin centered around E. The summation in equation (3) was carried out over the whole energy range for which energy deposition data were available, typically 0-300 eV. No ionizations were assumed to arise from energy deposition events with E < 10 eV.

The probability distribution $P\left(j|E\right)$ was approximated by a modified Poisson distribution

$$P\left(j|E\right) = \frac{\left(\Phi < j >\right)^{\Phi j}}{\Gamma\left(\Phi_j + 1\right)} \exp(-\Phi < j >)\Phi \qquad (4)$$

where $\langle j \rangle = E/W$, W is the mean energy expended per ion pair formed (32 eV), Γ is the gamma function, and $\Phi = F^{-1}$, where F is the Fano factor (0.30). This distribution has the same mean as the Poisson distribution but a variance that is reduced by the Fano factor. The energy dependence of W and F was neglected.

The results of the parameter calculations for protons and helium ions over a range of LETs are presented in Table I. Both parameters increase with increasing LET and have a maximum, which for q_1 occurs around 50 keV/μm and for q_2 around 170 keV/μm. The quality parameter q_2 exhibits a much stronger LET dependence than the parameter q_1.

5. Testing the Theory

So far, we have tested the two-compartment theory by predicting the dose and LET dependence of the

surviving fraction of synchronized G1/S and late-S phase V79 cells irradiated by 20 keV/μm and 40 keV/μm deuterons, 127 keV/μm helium-3 ions, and 250 kVp X-rays [7]. For the same LET, deuterons and protons as well as helium-3 and helium-4 ions have identical track structure, and thus the same q parameters should apply.

The predicted cell survival curves were calculated according to equation 1. The values of the parameters q_1 and q_2 were inferred from Table I. Fitting the equation $\ln(SF) = -(\alpha_1 + \alpha_2)D - \beta D^2$ to the low-LET survival data resulted in estimates for $\alpha_1 + \alpha_2$ and β, while fitting the equation $\ln(SF) = -(\alpha_1 q_1 + \alpha_2 q_2)D - \beta q_1^2 D^2$ to the high-LET data of 127 keV/μm helium ions resulted in an estimate for $\alpha_1 q_1 + \alpha_2 q_2$. From these estimates, the values of the individual parameters α_1 and α_2 were inferred. The resulting parameter values are listed in Table II.

Figure 2 shows predicted cell survival curves and observed data in comparison. A fairly good agreement between theory and experiment is seen. The predicted survival curves change their shape from linear-quadratic to nearly linear with change from low-LET to high-LET. Table III lists the predicted RBE values at a survival level of 10 % for both cell cycle phases as a function of LET. Independent of cell cycle phase, the RBE has a broad maximum in the LET range between 100 keV/µm and 200 keV/µm in agreement with experimental findings [7].

Table I – Radiation quality parameters for different radiation types.

Radiation Quality	Mean LET (keV/µm)	q_1	q_2
Low LET	< 1	1.00	1.00
4 MeV protons	9	1.22	1.48
2 MeV protons	16	1.18	1.37
1 MeV protons	26	1.32	2.93
0.5 MeV protons	40	1.34	4.62
0.3 MeV protons	59	1.27	7.45
20 MeV helium ions	32	1.30	2.59
16 MeV helium ions	40	1.34	2.78
10 MeV helium ions	51	1.31	4.57
4 MeV helium ions	103	1.06	8.66
3 MeV helium ions	127	0.93	9.87
2 MeV helium ions	167	0.72	10.89
1.2 MeV helium ions	230	0.51	9.37

Table II – LET-independent survival curve parameters for V79 cells.

Parameter	G1/S cells	Late-S cells
α_1 (Gy^{-1})	0.086	–0.017*
α_2 (Gy^{-1})	0.114	0.083
β (Gy^{-2})	0.046	0.016

* $\alpha_1 = 0$ was used for cell survival calculations.

Table III – Predicted RBE ($SF = 0.1$) for V79 cells as a function of radiation type and cell cycle phase.

Radiation Quality	Mean LET (keV/mm)	G1/S cells	Late-S cells
Low LET	< 1	1.00	1.00
4 MeV protons	9	1.26	1.27
2 MeV protons	16	1.21	1.22
1 MeV protons	26	1.61	1.70
0.5 MeV protons	40	1.96	2.15
0.3 MeV protons	59	2.52	2.95
20 MeV helium ions	32	1.53	1.60
16 MeV helium ions	40	1.60	1.67
10 MeV helium ions	51	1.93	2.12
4 MeV helium ions	103	2.68	3.25
3 MeV helium ions	127	2.90	3.60
2 MeV helium ions	167	3.05	3.89
1.2 MeV helium ions	230	2.58	3.32

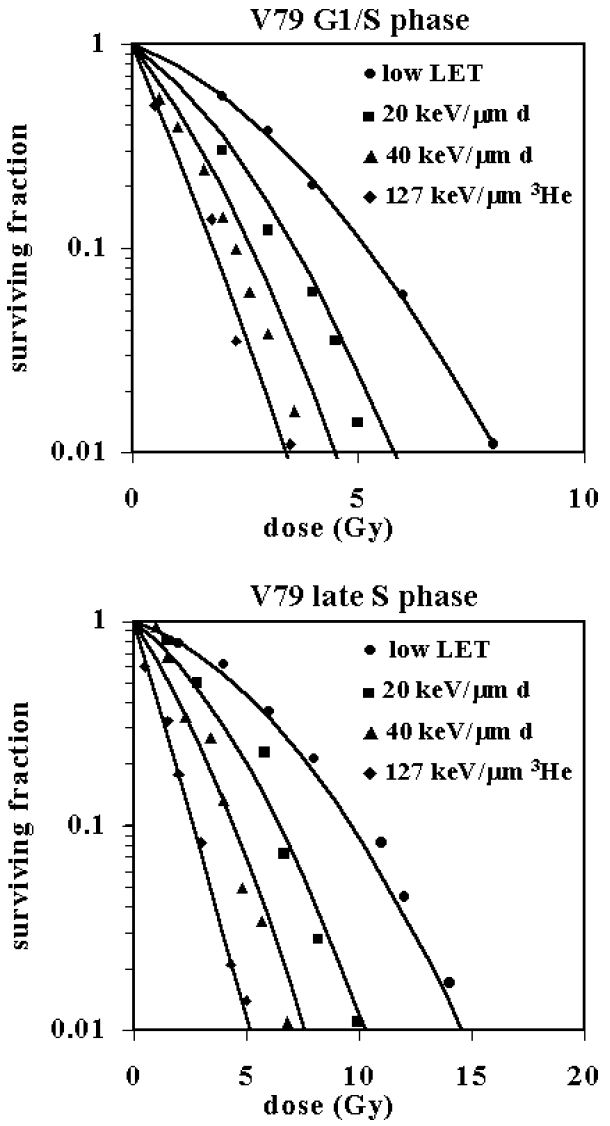

Fig. 2 – Comparison between predicted (lines) and observed (discrete points) cell survival fractions for V79 cells irradiated in G1/S phase or in late S phase.

6. Discussion and Conclusions

We have presented and tested a theory of radiation action, which is specifically based on nanodosimetric event spectra. The main feature of this theory is the distinction between repairable and irreparable clustered DNA damages, which are produced by low- and high-LET radiation albeit with different frequencies. The existence of irreparable damage and its correlation with the number of ionizations in nanodosimetric sites is hypothetical and remains to be proven experimentally. Since experimental nanodosimetric event spectra are currently unavailable, we have converted theoretical energy deposition spectra in cylindrical volumes to ionization-event spectra. The conversion was based on a hypothetical distribution function of number of ions for a given amount of energy deposited, which lacks experimental proof. Despite of these uncertainties, the two-compartment theory predicts quite accurately the main features of the dose- and LET-dependence of the surviving cell fraction of V79 cells irradiated in two different cell cycle phases.

Acknowledgements and disclaimer

This research effort was sponsored by the National Medical Technology Testbed Inc. (NMTB), under the U.S. Department of the Army Medical Research Acquisition Activity, Cooperative Agreement Number DAMD17-97-2-7016. The views and conclusions contained herein are those of the authors and do not necessarily reflect the position or the policy of the U.S. Army or NMTB. The work was partially supported by the German Minerva Foundation. S. Sh. was partially supported by the State of Israel, Ministry of Absorption. A.B. is the W.P. Reuther Professor of Research in the Peaceful use of Atomic Energy.

REFERENCES

[1] Little JB. Radiation carcinogenesis. Carcinogenesis 2000: 21; 397-404.

[2] Shchemelinin S, Breskin A, Chechik R, Colautti P, Schulte, R. First ionization cluster measurements on the DNA scale in a wall-less sensitive volume. Radiat Prot Dosim 1999: 82; 43-50.

[3] Nikjoo H, Goodhead DT, Charlton DE, Paretzke HG. Energy deposition in small cylindrical targets by monoenergetic electrons. Int J Radiat Biol 1991: 60; 739-56.

[4] Chapman JD, Doern SD, Reuvers AP, Gillespie CJ, Chatterjee A, Blakely EA, Smith KC, Tobias CA. Radioprotection by DMSO of mammalian cells exposed to X-rays and to heavy charged-particle beams. Radiat Environ Biophys 1979: 16; 29-41.

[5] Becker D, Razskazovskii Y, Callaghan MU, Sevilla MD. Electron spin resonance of DNA irradiated with a heavy-ion beam ([16]O[8+]): evidence for damage to the deoxyribose phosphate backbone. Radiat Res 1996: 146; 361-8.

[6] MRC mongographs. http://www.ragsu.har.mrc.ac.uk/nikjoo/mono/mono.htm.

[7] Bird RP, Rohrig N, Colvett RD, Geard C, Marino SA. Inactivation of synchronized Chinese Hamster V79 cells with charged-particle track segments. Radiat Res 1980: 82; 277-289.