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THE QUADRATIC MODEL FOR CELL SURVIVAL AFTER IRRADIATION: A NEW INTERPRETATION OF THE PARAMETERS

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THE QUADRATIC MODEL FOR CELL SURVIVAL AFTER IRRADIATION: A NEW INTERPRETATION OF THE PARAMETERS*

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ABSTRACT

In this paper we present the quadratic dose-response model for cell survival that allows the damage leading to a cell death to be either due to DNA single-strand breaks or DNA double-strand breaks, and the DNA double-strand breaks may be produced either by one ionizing particle of radiation or by two independent ionizing particles.

We show that the proposed interpretation of the parameters is more comprehensive than that given by Leenhouts and Chadwick (1978) and is consistent with the results of fractionated-irradiation and post-irradiation treatment studies. We feel that the proposed model may be useful in radiation protection experiments as well as in understanding other biological and genetic effects that may be caused by DNA single-strand or DNA double-strand breaks.

Key words: Biological effect; Fractionated-irradiation; Post-treatment effect; Repair mechanism.

1. INTRODUCTION

Let y denote the probability of survival (corrected for natural survival) corresponding to a dose d of radiation. Then the quadratic model

$$y = \exp(-\alpha d - \beta d^2), \tag{1}$$

has been often used to represent the dose-response function in radiobiological studies (Keller and Rossi, 1972; Chadwick and Leenhouts, 1973; Douglas and Fowler, 1976; Leenhouts and Chadwick, 1978; Peres and Koo, 1981).

Chadwick and Leenhouts (1973) developed this model under the assumption that the cell death is caused by the DNA double-strand breaks only. For the parameters of this model, Leenhouts and Chadwick (1978) gave the following interpretation: α represents the contribution to the cell death due to DNA double-strand breaks produced by one ionizing particle of radiation, and β represents the contribution to the cell death due to DNA double-strand breaks produced by two-independent ionizing particles, one for each strand.

However, there is a considerable evidence to show that the cell death may be caused by two independent processes, namely, DNA single-strand breaks or DNA double-strand breaks (Bender and Wolff, 1961; Bender and Gooch, 1962; Tym and Todd, 1964). Recently, Peres and Narula (1985b) have given a derivation for the quadratic model based on the following assumptions:

1. Within the nucleus of each cell there are n sites. When at least one of these sites is damaged it may cause the cell death.

2. At each site the damage that results in the cell death is either a DNA single-strand break or a DNA double-strand break.

3. The DNA double-strand break can occur either by the passage of an ionizing particle of radiation very close to the DNA or by the action of two independent ionizing particles passing close to the DNA.

4. Although a small number of DNA strand breaks may arise from direct action of ionizing particles on the DNA molecule itself, the large majority of strand-breaks arise from indirect action through water radicals created by the radiation in the surroundings close to the DNA molecule.

5. The number of ionizing particles that pass close to a nucleotide and may or may not produce DNA strand-breaks follow a Poisson distribution.

Observe that the first four assumptions are radiobiological.

Our objectives in this paper are: (i) to present the model and the interpretation of its parameter (Section 2); (ii) to show that the proposed interpretation of the parameters is consistent with the results of fractionated-irradiation and post-irradiation treatment studies (Section 3); and (iii) to give further interpretation and uses of the model (Section 4).

2. THE MODEL AND AN INTERPRETATION OF ITS PARAMETERS.

Let

n denote the number of sites in a cell,

ω denote the probability per unit dose that an ionizing particle will pass close to the DNA molecule,

Ω denote the probability that an ionizing particle passing close to the "first" DNA strand also passes close to the "second"

DNA strand. It depends upon the quality of radiation and the geometry of the DNA molecule.

k denote the probability that an ionizing particle passing close to a nucleotide leads to a DNA strand-break. It depends upon the quality of radiation and the chemical make up (see assumption 4) of the nucleus of the cell.

f_1 denote the proportion of DNA single-strand breaks which are *not* repaired and may lead to a cell death,

f_{12} denote the proportion of DNA single-strand breaks which are *not* repaired before a second single-strand break converts it into a double-strand break that may lead to a cell death,

f_2 denote the proportion of DNA double-strand breaks which are *not* repaired and may lead to a cell death,

p_1 denote the probability that the cell death is caused by DNA single-strand breaks, and

p_2 denote the probability that the cell death is caused by DNA double-strand breaks,

Then the model can be written as the quadratic model in (1) where

$$\alpha = n\left[2p_1f_1k\omega(1-k\Omega) + p_2f_2k^2\omega\Omega\right], \tag{2a}$$

and

$$\beta = n\left[p_2f_{12}f_2k^2\omega^2(1-k\Omega)^2\right]. \tag{2b}$$

The interested reader may refer to Peres and Narula (1985b) for further details.

To interpret α, we rewrite the expression (2a) for α (without n) as

$$2p_1f_1k\omega(1-\Omega)+2p_1f_1k(1-k)\omega\Omega+p_2f_2k^2\omega\Omega. \tag{3}$$

The first term, $2p_1f_1k\omega(1-\Omega)$, represents the probability per unit dose that an ionizing particle passing near a single-strand of DNA breaks it, the break is not repaired and the cell dies. The second term, $2p_1f_1k(1-k)\omega\Omega$, denotes the probability per unit dose that an ionizing particle passing near two-strands of DNA breaks one strand but does not break the other strand; the broken strand is not repaired and the cell dies. The third term $p_2f_2k^2\omega\Omega$, represents the probability per unit dose that an ionizing particle passing near two-strands of DNA produces a double-strand break which is not repaired and results in the cell death. Thus, parameter α represents the contribution to the cell death due to DNA single-strand breaks and due to DNA double-strand breaks which are caused by one ionizing particle of radiation.

To interpret β, we rewrite the expression (2b) for β (ignoring n) as

$$p_2\left[f_2\{f_{12}k\omega(1-k\Omega)\}k\omega(1-k\Omega)\right]. \qquad (4)$$

Using the interpretation of the first two terms of α in (3), the term $\{f_{12}k\omega(1-k\Omega)\}$ in (4) represents the probability per unit dose that an ionizing particle breaks a single DNA strand which is not repaired before a second DNA strand break converts it into a DNA double-strand break. Thus, the expression $\left[f_2\{f_{12}k\omega(1-k\Omega)\}k\omega(1-k\Omega)\right]$ represents the probability of DNA double-strand breaks caused by two independent ionizing particles. So, the parameter β represents the contribution of DNA double-strand breaks produced by two independent ionizing particles.

Observe that if $p_1=0$, that is, the only damage leading to cell death is the DNA double-strand breaks, the parameters α and β

have the same structure and interpretation as given by Leenhouts and Chadwick (1978). In other words, the interpretation of the parameters α and β given by Leenhouts and Chadwick (1978) is a special case of the proposed interpretation of the parameters of the quadratic model in (1).

From the expression of the model in (1), it is clear that an increase in survival probability (for a given dose) can be obtained by either decreasing α or β or both. There is evidence (Resnick and Martin, 1976) that the repair mechanism of DNA single-strand breaks is more efficient than that of DNA double-strand breaks. Since in the proposed model, parameter α represents the contribution to cell death due to DNA single-strand breaks and DNA double-strand breaks whereas the parameter β represents the contribution to the cell death only due to DNA double-strand breaks, we would expect a larger change in α than in β from the dose fractionated-irradiation and the post-irradiation treatment studies because such treatments effect the repair mechanism of the cells.

3. DATA ANALYSIS

3.1. Fractionated-Irradiation Study

We reanalyzed that data from the fractionated irradiation study of Sankaranarayanan and Volkers (1980). The estimates of α and β for their data for unfractioned, two-fractioned and three-fractioned irradiation regimes are given in Table 1. From Table 1, we

Insert Table 1 about here

observed that α and β both decrease with fractionated dose; however,

as expected, the reduction in α is much larger compared to that in β. For example, the reduction in α for three-fractionated irradiation relative to the unfractioned-irradiation is 64.93% compared to 34.47% for β. Hence, the proposed interpretation of the parameters is consistent with the results of Table 1.

3.2. Post-Irradiation Treatment Study

We reanalyzed the data from the post-irradiation treatment study of Sankaranarayanan (1969). The estimates of α and β for the three groups of his experiments, namely, (i) irradiation in nitrogen, N_2 followed by either N_2 or oxygen, O_2 post-treatment, (ii) irradiation in O_2 followed by either N_2 or O_2 post-treatment, and (iii) irradiation in air followed by either N_2 or air post-treatment, are given in Table 2. When we compare the first and the second ex-

Insert Table 2 about here

periment in each group, the estimates of parameter β are very similar for the two experimental conditions but the estimate of parameter α in the second experimental condition in each group is about one half of that for the first experimental condition. Thus, the proposed interpretation of the parameters is consistent with the results of Table 2.

The estimates of parameters α and β in Tables 1 and 2 were obtained by the nonlinear least squares procedure. Recently, Peres and Narula (1985a) have proposed a simple closed form approximation for estimating these parameters.

4. SOME REMARKS

1. We distinguish two sets of parameters used in developing the quadratic model. One set of parameters n, ω, Ω, k, f_1, f_{12}, and f_2 are related to the production of DNA single-strand and DNA double-strand breaks that may or may not cause the cell death, i.e., these parameters are related to the potential damage produced by radiation. The second set of parameters, p_1 and p_2, relates the potential damage to the final biological effect. These parameters depend upon the cell type, the biological system, and the final effect under study (see the next remark). Different irradiation conditions should not change the parameters.

2. The final effect of radiation can be biological (survival or cancer) or genetic (mutation or chromosome abberation). Hence, the proposed model may be used for any biological or genetic effect if it can be assumed that the effect is produced by DNA single-strand breaks or DNA double-strand breaks. However, in order to apply the model to other biological or genetic effects, it is important to appropriately redefine the parameters p_1 and p_2.

3. If for an experimental condition we can assume that $p_1=0$, i.e., the only cause of cell death is due to DNA double-strand breaks, the parameters α and β have the same structure and interpretation as given by Leenhouts and Chadwick (1978). However, if $p_2=0$, the model in (1) reduces to

$$y = \exp(-\alpha d).$$

As mentioned in Section 2, the parameter Ω depends upon the radiation quality. For very low LET ($\Omega=0$) the parameter α is still different from zero. Since $\alpha = 2p_1 f_1 k\omega n$, it reflects the contribution

of the DNA single-strand breaks. That is, the dose-response curve still has a non-zero slope at a very low dose. This information may be very important and useful for radiation protection in organism where the cell death may be caused by DNA single-strand breaks.

4. The parameters f_1, f_{12}, and f_2 are related to the repair mechanism of the DNA and therefore depend upon the metabolic activity of the cell, the cell stage and the time available for repair. Since the repair mechanism for a DNA single-strand break is more efficient than that for the DNA double-strand breaks (Resnick and Martin, 1976), we would expect $f_2 > f_1$ and $f_2 > f_{12}$. These parameters can be very important and useful in the explanation of variation in the survival probability in any experiment in which a treatment may effect the repair mechanism of the cell.

REFERENCES

Bender, M. A. and Gooch, P. C. (1962). The kinetics of x-ray survival of mammalian cells *in vitro*. *International Journal of Radiology and Biology* 5, 133-145.

Bender, M. A. and Wolff, S. (1961). X-ray-induced chromosome aberrations and reproductive death in mammalian cells. *The American Naturalist* 95, 39-52.

Chadwick, K. H. and Leenhouts, H. P. (1973). A molecular theory of cell survival. *Physics in Medicine and Biology* 18, 78-87.

Douglas, B. G. and Fowler, J. F. (1976). The effect of multiple small doses of x-rays on skin reaction in the mouse and a basic interpretation. *Radiation Research* 66, 401-426.

Kellerer, A. M. and Rossi, H. H. (1972). The theory of dual radiation action. *Current Topics in Radiation Research Quarterly* 8, 85-158.

Leenhouts, H. P. and Chadwick, K. H. (1978). The crucial role of DNA double-strand breaks in cellular radiobiological effects. In *Advances in Radiation Biology, Vol.7*. J. T. Lett and H. Alder (eds.), 56-101. New York, Academic Press.

Peres, C. A. and Koo, J. O. (1981). A comparison of two-component and quadratic models to assess survival of irradiated stage-7 oocytes of *Drosophila melanogaster*. *Mutation Research* 91, 341-346.

Peres, C. A. and Narula, S. C. (1985a). A simple procedure to determine the parameters of a quadratic dose-response model. Research Report Nº IME-85 , University of São Paulo, São Paulo, Brasil.

Peres, C. A. and Narula, S. C. (1985b). A new derivation of the

quadratic dose-response model for cell survival in radiobiological studies. Research Report IME-85 , University of São Paulo, São Paulo, Brasil

Resnick, M. A. and Martin, P. (1976). The repair of double-strand breaks in the nuclear DNA of saccharomyces cerevisiae and its genetic control. *Molecular General Genetics 143*, 119-129.

Sankaranarayanan, K. (1969). The effects of oxygen and nitrogen post-treatments on the mortality of Drosophila eggs irradiated as stage-7 oocytes. *Mutation Research 7*, 357-368.

Sankaranarayanan, K. and Volkers, W. S. (1980). Exposure fractionation effects of x-ray induced dominant lethals in immature (stage-7) oocytes of *Drosophila melanogaster*: A reanalysis. *Mutation Research 69*, 249-262.

Tym, R. and Todd, P. W. (1964). The sensitization by iododeoxyuridine of cultured human cells to the lethal effects of x-rays and heavy ions. *International Journal of Radiology and Biology 8*, 589-604.

LIST OF TABLES

TABLE 1

Radiation Regimes	Estimated values of α	β
Unfractioned	0.1075	0.0470
Two Fractions	0.0625	0.0374
Three Fractions	0.0371	0.0308

TABLE 2

Experimental Condition	Estimated values of α	β
$N_2 - R - N_2$	0.0964	0.0092
$N_2 - R - O_2$	0.0452	0.0094
$O_2 - R - N_2$	0.2062	0.0764
$O_2 - R - O_2$	0.1081	0.0619
Air - R - N_2	0.1666	0.0335
Air - R - Air	0.0891	0.0273

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