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THE MICRODOSIMETRIC LINK BETWEEN ONCOGENIC TRANSFORMATION DATA WITH NEUTRONS AND CHARGED PARTICLES

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Abstract — One of the most important challenges in biophysics is to predict the variation of biological effectiveness with radiation quality in terms of a physical quantity that can be measured or deduced from experiment. In recent years, a substantial body of data had been accumulated at the Radiological Research Laboratory involving cell lethality and oncogenic transformation, caused by: (a) Monoenergetic neutrons with energies from 200 keV to 14 MeV. (b) Charged particles in the track segment mode, with defined LET values from 10 to 150 keV.μm^{-1}. Microdosimetric spectra have also been generated for these radiation beams. This body of data provides, for the first time, the possibility of investigating the best physical specifier of radiation quality in relation to a relevant endpoint, namely oncogenic transformation. Eight different biophysical parameters were investigated to see which, if any, were consistent with, and predictive of, the data. It was concluded that the dose-averaged quantities LET_D (restricted or unrestricted) and y_D (1 μm or 25 nm site size) are the best predictors of relative transformation rates for different radiations.

INTRODUCTION

Starting more than two decades ago, several systematic studies were made on the variation of biological effectiveness with radiation quality for charged particles[1,2] and for neutrons[1,3,4]. The endpoints were *in vitro* cell survival in mammalian cells[1,2,3] or growth inhibition in *Vicia faba* seedlings[4]. Subsequent analyses attempted to find a single parameter describing the radiation quality, which would be predictive of these data. Examples were the parameter y^* (dose-averaged lineal energy corrected for saturation[5]) or z^{*2}/β^2 (corresponding to a restricted LET[6]).

As pointed out by Edwards[7], an ideal data set to consider would be that obtained for a narrow radiation quality range (e.g. charged particles in the 'track segment' mode) and also (for the same endpoint) for a broad radiation quality range (e.g. neutrons). At that time (1980), only one data set of that type was available, that of Barendsen[1], for T1 kidney cell survival. Almost a decade later, such a data set does now exist for the endpoint of oncogenic transformation in the C3H 10T1/2 system[8,9]. Although of questionable direct applicability to the question of human carcinogenesis, these data must surely be of more relevance than those for an *in vitro* cell survival endpoint. In this paper, we analyse the transformation data in terms of a variety of model-based parameters, to see whether any are consistent with the data.

THE BIOLOGICAL DATA SET

The data analysed here, all of which were obtained at the Radiological Research Accelerator Facility of Columbia University, have been reported recently[8,9]. The neutron data[8] consist of induced transformation frequencies (per surviving cell) for exponentially growing C3H 10T1/2 cells, as a function of dose, for eight different neutron energies between 230 keV and 13.7 MeV. The 'track segment' data set[9] involves the same endpoint, but irradiations were performed with accelerated protons, deuterons, or ^{3}He ions. The LETs of the ions were 10, 40, 80, 120, and 150 keV.μm^{-1}. (The 150 keV.μm^{-1} data were not reported in Reference 9). In both sets of experiments, transformation data were also obtained with 250 kVp X rays.

The entire data set (for neutrons, charged particles, and both sets of X rays) were analysed in a consistent way by fitting them, using the maximum likelihood criterion, to the model

$$Y_i(D) = \alpha_i D + \beta D^2 \quad (1)$$

where $Y_i(D)$ is the induced transformation frequency per surviving cell at a dose D of radiation type i, and the $[\alpha_i, \beta]$ are n+1 free parameters for n different radiations. The data set were also fitted to the relation

$$Y_i(D) = \alpha_i D + \beta_i D^2 \quad (2)$$

where the $[\alpha_i, \beta_i]$ are 2n free parameters. The fit was little improved in the second case, model 1 could not be rejected using the appropriate F test, so the $[\alpha_i]$ from model 1 were taken to represent the initial slopes of the data.

CALCULATION METHODS

The following parameters have been calculated

for the various radiations described in the last section:

L_∞ : track-averaged LET[1];
L_D : dose-averaged LET[10];
y_D : dose-averaged lineal energy[11] in 1 μm diameter site;
y^* : dose-averaged lineal energy corrected for saturation[11] in 1 μm diameter site;
Q(LET) : quality factor based on L_∞, as set out in the 1954 Handbook 59[12];
Q(y) : quality factor based on lineal energy, y, as set out in the 1986 ICRU Report 40[13];
$L_{100,D}$: dose-averaged restricted LET (100 eV cut-off), approximated[14] (see below) by y_D in a 25 nm site size;
$\sum_j \int \phi_j(E) p_j(E) dE/K_n$: (defined below) relative effectiveness per unit dose in the grain count regime of the Katz model[6].

For ions in the track-segment mode, all the above parameters are simple to calculate. For neutrons, however, the situation is more complex. Required are the secondary charged particle production energy spectra, $\phi_j(E)$, for different secondary charged particles, j, produced by the various energy neutrons; these are briefly described by Zaider and Brenner[15]. For the calculation of y_D, y, Q(y) and $L_{100,D}$, these must be used in conjunction with a computer code[15] to calculate lineal energy spectra based on Caswell's concepts of insiders, starters, crossers, and stoppers.

The quantity mentioned above as the relative effectiveness per unit dose in the grain-count regime of the Katz model[16] is actually

$$\sum_j \int \phi_j(E)\, p_j(E)\, dE/K_n$$

where

$$p_j(E) = \{1-\exp[-z_j^{*2}(E)/\beta_j^2(E)\kappa]\}^m$$

z_j^* being the effective charge of ion j, K_n being the neutron kerma factor, and [m, κ] being a parameter set, taken from an analysis of 10T1/2 transformation data at the BEVALAC[17].

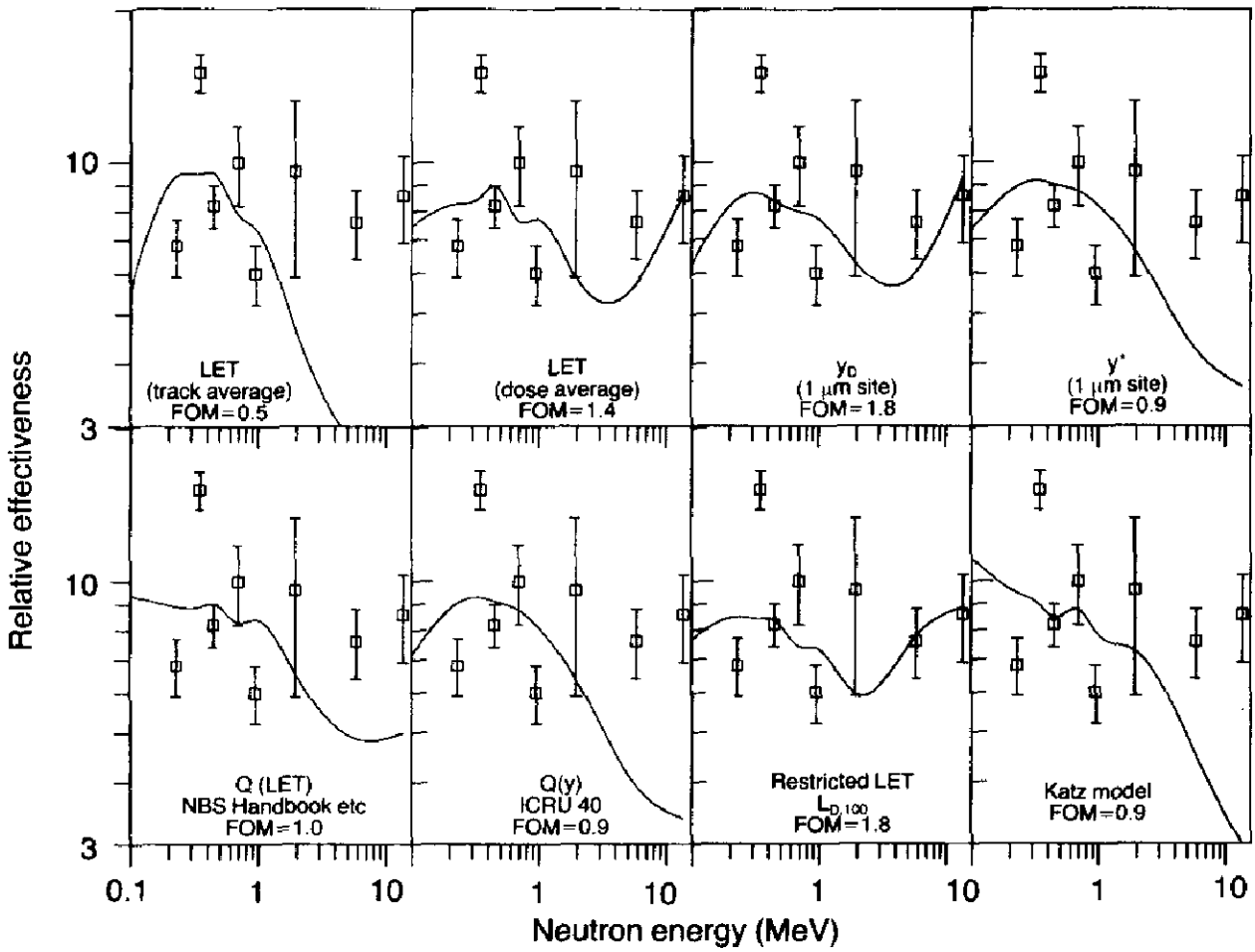

Figure 1. The points are the measured relative effectiveness of different energy neutrons for causing oncogenic transformation in C3H 10T1/2 cells[8]. The curves are derived from the eight different models described in the text and have each been adjusted in magnitude to give the best agreement with the data, in the least-squares sense. In each case, the figure of merit (FOM) is proportional to the reciprocal of the minimum value of the sum of squares.

The quantity $L_{100,D}$ has been suggested as a good predictor of radiation quality[18]. It is not directly measurable, and not convenient to calculate; however, Blohm and Harder[14] have suggested that the dose averaged lineal energy, y_D, in 25 nm diameter spheres, might be a good approximation. We have therefore calculated y_D in this site, using the LET based CSDA approximation. At such small sites, particularly for higher energy neutrons, the effect of straggling will begin to play an important role[11]. However, we were encouraged that a calculation in the LET approximation for 6 MeV neutrons incident on a target of mean path length 25 nm was in good agreement (y_D = 79 keV.μm^{-1}) with measurements (80±10 keV.μm^{-1}) of the same quantity using the variance-covariance technique[19]. For 14 MeV neutrons, where the LET approximation will certainly break down, we have used the measurement of Goldhagen *et al*[20] (114 keV.μm^{-1} at 28 nm).

RESULTS

Two questions have been addressed: First, are any of the biological predictors mentioned above compatible with the variation in transformation efficiency exhibited by the various energy (0.23 to 14 MeV) neutrons? Second, are any of these 'predictors' consistent with the large variation in transformation efficiency as a function of radiation quality exhibited by the entire data set (neutrons and 'track segment' charged particles)?

For the neutrons, there are quite large error bars on the relative effectiveness data. However, the general trend in Figure 1 is clear, namely that there is not a great variation in effectiveness from energy to energy, and there does not seem to be a rapid fall-off in effectiveness at high energies, as is evident, for example, in V-79 cell survival data[3].

'Best' fits to the data for the various predictors were obtained by applying a multiplicative free scaling factor to the predictions – in other words, the predictions were moved up and down (on a log scale) until the minimum deviation from the data points (in the least-squares sense) was found. The reciprocal of the minimum sum of squares was then taken to represent a 'figure of merit' (FOM) for that predictor. The results for neutrons are shown in Figure 1. The best predictors were either y_D (in either site size) or dose averaged LET, which had significantly better figures of merit than had the other parameters.

To investigate the consistency of the entire data set, covering a wide range of radiation qualities, with the various predictors, the initial slopes (or maximum RBE), α_i, were plotted against the values of the predictors for the radiations in question. The idea is to see which parameters indicate a unique relationship between that parameter and biological effectiveness. A slightly smaller set of parameter types was used in this analysis, the Katz parameter and $L_{100,D}$ being excluded on the pragmatic grounds that they are neither measurable nor easily calculable, and thus may play a limited role in the radiation protection considerations of interest here. The results are shown in Figures 2 and 3. Again, it appears that y_D or dose averaged LET are the parameters of choice, both indicating single valued properties, in contrast to all of the other parameters.

CONCLUSIONS

For the endpoint of oncogenic transformation in C3H 10T1/2 cells, either of the dose averaged quantities, y_D (in either site size) or L_D (unrestricted or restricted), are reasonable parameters for use in the prediction of RBE and/or quality factors. The conventional weighted quantities, Q(L) or Q(y) or y* are significantly less desirable in this regard, as are track averaged LET and z^2/β^2.

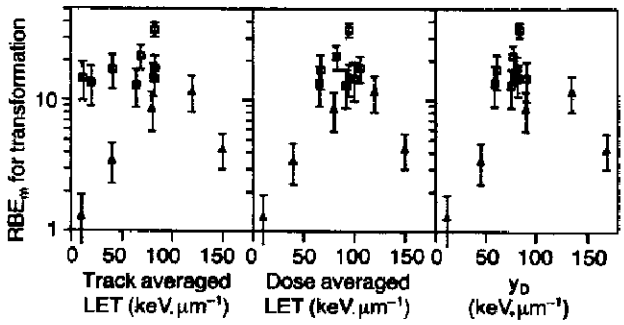

Figure 2. Maximum RBE (based on initial slopes of dose responses) derived from track-segment data (▲)[9] and from neutron data (□)[8]. The RBEs, when plotted against LET (dose averaged) or y_D (1μm site size), yield a roughly single-valued function; this is not the case for LET (track average).

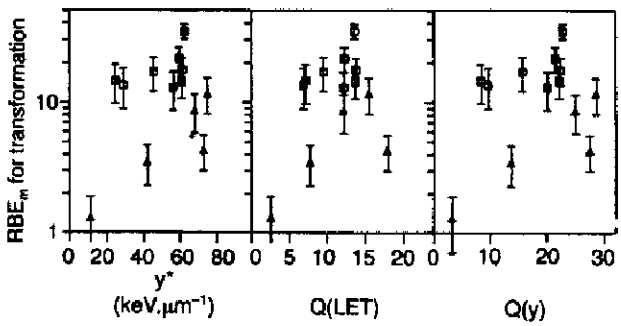

Figure 3. As Figure 2; the data when plotting against any of these three abscissae, do not yield a single valued function.

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REFERENCES

1. Barendsen, G. W. *Mechanism of Action of Different Ionizing Radiations on the Proliferative Capacity of Mammalian Cells.* In: Theoretical and Experimental Biophysics (New York: Marcel Dekker), p. 167 (1967).
2. Todd, P. W. *Reversible and Irreversible Effects of Ionizing Radiations on the Reproductive Integrity of Mammalian Cells Cultured In Vitro.* UCRL report no. 11614 (Lawrence Livermore Radiation Laboratory) (1964).
3. Hall, E. J., Novak, J. K., Kellerer, A. M., Rossi, H. H., Marino, S. A. and Goodman, L. J. *RBE as a Function of Neutron Energy. I. Experimental Observations.* Radiat. Res. **64**, 245-255 (1975).
4. Hall, E. J., Rossi, H. H., Kellerer, A. M., Goodman, L. and Marino, S. *Radiobiological Studies with Monoenergetic Neutrons.* Radiat. Res. **54**, 431-443 (1973).
5. Kellerer, A. M. and Rossi, H. H. *The Theory of Dual Radiation Action.* Curr. Top. Radiat. Res. Q. **8**, 85-158 (1972).
6. Katz, R. *RBE, LET and z^2/β^2.* Health Phys. **18**, 175 (1970).
7. Edwards, A. A. *LET, ζ^* or z^2/β^2. Which is the Best Specification of Radiation Quality?* In: Proc. 7th Symp. on Microdosimetry (London: Harwood Academic) (1981).
8. Miller, R. C., Geard, C. R., Brenner, D. J., Komatsu, K., Marino, S. A. and Hall, E. J. *Neutron-Energy-Dependent Oncogenic Transformation of C3H 10T1/2 Mouse Cells.* Radiat. Res. **117**, 114-127 (1989).
9. Hei, T. K., Komatsu, K., Hall, E. J. and Zaider, M. *Oncogenic Transformation by Charged Particles of Defined LET.* Carcinogenesis **9**, 747-750 (1988).
10. International Commission on Radiation Units and Measurements. *Lineal Energy Transfer,* ICRU Report no. 16 (Washington, DC: ICRU Publications) (1970).
11. International Commission on Radiation Units and Measurements. *Microdosimetry,* ICRU Report no. 36 (Bethesda, MD: ICRU Publications) (1983).
12. National Bureau of Standards. *Permissible Dose from External Sources of Ionizing Radiation.* Handbook 59 (Washington, DC: National Bureau of Standards) (1954).
13. International Commission on Radiation Units and Measurements. *The Quality Factor in Radiation Protection,* ICRU Report no. 40 (Bethesda, MD: ICRU Publications) (1986).
14. Blohm, R. and Harder, D. *Restricted LET: Still a Good Parameter of Radiation Quality for Electrons and Photons.* Radiat. Prot. Dosim. **13**, 377-381 (1985).
15. Zaider, M. and Brenner, D. J. *On the Microdosimetric Definition of Quality Factors.* Radiat. Res. **103**, 302-316 (1985).
16. Armstrong, T. W. and Chandler, K. C. *Calculations Related to the Application of Negatively Charged Pions in Radiotherapy: Absorbed Dose, LET Spectra, and Cell Survival.* Radiat. Res. **58**, 293-328 (1974).
17. Waligorski, M. P. R., Sinclair, G. L. and Katz, R. *Radiosensitivity Parameters for Neoplastic Transformations in C3H 10T1/2 Cells.* Radiat. Res. **111**, 424-437 (1987).
18. Harder, D., Blohm, R. and Kessler, M. *Restricted LET Remains a Good Parameter of Radiation Quality.* Radiat. Prot. Dosim. **23**, 79-82 (1988).
19. Lindborg, L., Kliauga, P., Marino, S. and Rossi, H. H. *Variance-Covariance Measurements of the Dose Mean Lineal Energy in a Neutron Beam.* Radiat. Prot. Dosim. **13**, 347-351 (1985).
20. Goldhagen, P., Randers-Pehrson, G., Marino, S. A. and Kliauga, P. *Variance-Covariance Measurements of y_D for 15-MeV Neutrons in a Wide Range of Site Sizes.* Radiat. Prot. Dosim. **31**, 1-4, 167-170 (1990) (This issue).