BIOPHYSICAL ANALYSIS OF RADIATION-INDUCED CHROMATID AND CHROMOSOME ABERRATIONS AT LOW DOSES AND DOSE RATES

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INTRODUCTION

In the present study, two sets of experimental data have been analyzed: (i) *in vitro* and *in vivo* exposures of human blood lymphocytes to alpha particles from short-lived radon decay products (1,2), and (ii) *in vitro* irradiation of rat hepatocytes with gamma radiation (with and without pre-irradiation) (3). The biophysical multi-stage model for radiation-induced chromosomal damage used in these analyses is derived from earlier models for radiation-induced transformation (4,5) and liver carcinogenesis (6).

BIOPHYSICAL MODEL

A biophysical model for the production of radiation-induced chromatid and chromosome aberrations as a function of dose or dose rate has been developed, which is based on experimentally observable cellular mechanisms, such as the formation of single and double strand breaks or cellular inactivation. In this multi-stage model, a sequence of five states is assumed in the development of a cell from the initial unirradiated level (state 0) to a cell exhibiting chromosomal damage (state 4) (Figure 1). The intermediate steps in this sequence of events are: production of an unspecific DNA single strand break (rate k_{01}); production of a second specific DNA single strand break (k_{12}); interaction of both DNA single strand breaks to form a double strand break (rate k_{23}); division-related fixation of the DNA double strand break thereby producing chromosome aberrations (rate k_{34}); and, division-related fixation of two single strand breaks leading to chromatid aberrations (rate k_{24}=m). Single and double strand break formation may be reduced by adaptive mechanisms, while actual breaks may be repaired (rates k_{10}, k_{21} and k_{30}). Cells in the various states can be removed by radiation-induced cell death (rate k_d) and apoptosis (rate k_a), and increased by mitosis (rate m). In case of alpha irradiation, double strand breaks can also be produced by single alpha particle intersections (rate k_{03}). The values for the transition rates between the various states in this model were derived from *in vitro* cellular experiments.

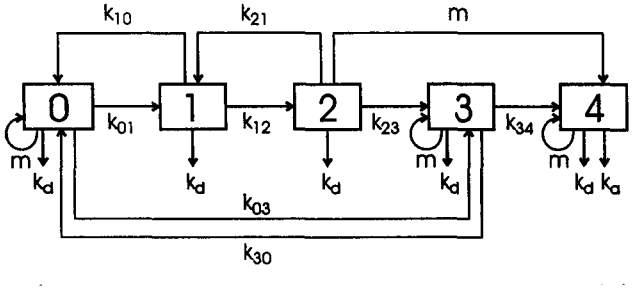

Figure 1. Biophysical multi-stage model for the analysis for radiation-induced chromatid and chromosome aberrations produced by alpha and gamma irradiation. Transition rates are described in related text.

ANALYSES OF EXPERIMENTAL DATA

In the first analysis, chromosome aberrations in human blood lymphocytes were exposed to short-lived radon decay products under *in vitro* irradiation conditions (1). Blood samples were irradiated by ^{214}Po alpha particles at doses between 0.02 and 26.9 mGy. The aberration data were collected from 11 experiments conducted during the period 1984 to 1992; a total of 64816 metaphases was scored in eight collaborating laboratories. Figure 2 illustrates the total chromosomal aberrations (dicentrics, rings, interstitial and terminal deletions) as a function of dose for blood samples taken between 1984 and 1986, i.e., prior to the Chernobyl accident. The data plotted here are based on 10687 scored metaphases. After a steep linear increase at very low doses, the aberration frequency gradually drops with increasing dose. The comparison between with these experimental data and our model simulations indicates that the biophysical model developed here is capable of reproducing the functional form of the experimentally observed dose-response curve.

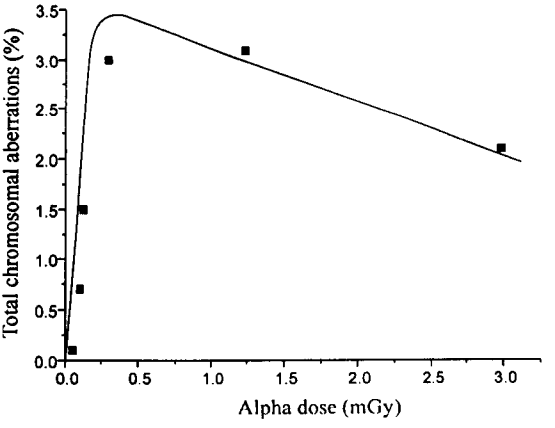

Figure 2. Total chromosomal aberrations (dicentrics, rings, interstitial and terminal deletions) in human blood lymphocytes for low dose *in vitro* alpha particle irradiation. The full squares refer to the experimental data, while the full line represents the model simulations.

A similar dose-reponse relationship has been reported for low dose and dose rate *in vivo* radon progeny irradiation of blood lymphocytes in miners and medical staff working in the Badgastein thermal gallery: total chromosome aberrations first rise linearly with dose up to about 7 mGy/year and then decrease with increasing alpha dose (2).

In the second analysis, primary cultures of adult rat hepatocytes were irradiated with ^{60}Co gamma radiation at much higher doses of 0.01, 0.1, 1 and 5 Gy at a dose rate of 33 Gy/h (3). In order to study potential effects of adaptive response mechanisms, the same set of doses was also applied to hepatocyte cultures pre-irradiated with 2.5, 10, 100 and 200 mGy 24 hours prior to exposure. As shown in Figure 3, induction of chromosomal aberrations for both normal and pre-irradiated cells rises sharply with dose in the low dose region and then remains level at higher doses. Most importantly, however, all pre-irradiation doses caused a significant reduction of chromosomal aberrations, which was highest for a pre-irradiation dose of 2.5 mGy. Our theoretical predictions of the shape of the dose-response relationship as well as of the effect of the induction of adaptive response mechnisms by pre-irradation are consistent with the experimental evidence.

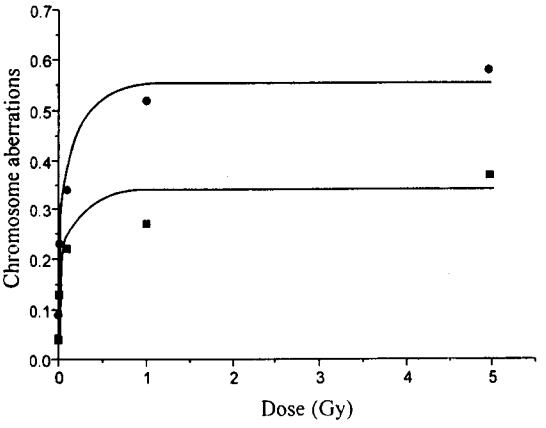

Figure 3. Total chromosomal aberrations in primary rat hepatocytes by *in vitro* gamma irradiation. The full circles (without pre-irradiation) and full squares (2.5 mGy adaptive dose) denote the experimental data; the full lines refer to the corresponding model simulations.

CONCLUSIONS

The three sets of experimental data analyzed in this study cover different dose regions (very low, low and high), cell types (lymphocytes, hepatocytes), radiations (alpha, gamma) and irradiation conditions (*in vitro*, *in vivo*, pre-irradiation). Despite these differences, a consistent pattern emerges. If chromosome aberrations are plotted as a function of dose, four distinct regions can be observed: First, at the lowest doses, no chromosomal damage can be statistically detected; above a certain dose level, the frequency of aberrations increases almost linearly with dose; following the induction of adaptive mechanisms, the dose-response may either exhibit a plateau or even decrease, depending on pre-exposure and dose rate; and, finally, chromosomal damage rises again at sufficiently high cellular doses.

Comparing our theoretical results with these three sets of experimental data, we may conclude that our model correctly predicts both the shape of the dose-response curve as well as the action of adaptive response mechanisms induced by pre-irradiation.

ACKNOWLEDGEMENTS

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