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A model for low dose effects of low-LET radiation delivered at high dose rates

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Abstract

In vitro studies show that protective tumour-reducing effects occur for low dose rates (mGy per minute). To account for these phenomena, we have previously developed stochastic and deterministic multi-stage cancer models that include radiation-induced adaptations in DNA repair processes and radical scavenging. Here, these models are extended to account for the induction of radioprotective mechanisms for low doses of low LET radiation delivered at high dose rates. Cellular adaptations in DNA repair are related to temporal changes in the amount of DNA damage in a cell. The combined effects of endogenous DNA damage, background radiation and artificial irradiation are considered.

Keywords

endogenous processes; high dose rate; low dose; radioprotective mechanisms; repair accuracy

1 Introduction

The current study is an extension of an ongoing collaborative effort, with the aim to improve model-based risk estimations for low doses of low-LET radiation. Earlier studies were restricted to low-LET radiation delivered at low dose rates (Schöllnberger et al., 2004; Schöllnberger et al., in press). As in the previous work, the new model accounts for simple and complex damage formed by endogenous processes and ionising radiation. The induction of DNA repair processes can also be simulated. Adaptations in DNA repair mechanisms provide one plausible explanation for the reductions in neoplastic transformation below the spontaneous level as observed in the low dose in vitro experiments of Azzam et al. (1996), Redpath and Antoniono (1998) and Redpath et al. (2001, 2003). In this paper, we give a short description of a new model to relate adaptations in the accuracy of DNA damage repair to temporal changes in the amount of unrepaired damage, during and after exposure to ionising radiation. The current paper presents model simulations of the amount of simple and complex damage induced by low doses of low-LET radiation delivered at high doses rates, and examines the effects of inducible DNA repair on mutation rates. Future work will

focus on extending the approach to relate radiologically induced changes in the radical scavenging capacity to the amount of transiently unrepaired DNA damage and to integrate the mutation models into the two-stage cancer model.

2 Materials and methods

For some of our risk estimations, we have been using the two-stage model (Moolgavkar, 1978; Moolgavkar and Venzon, 1979) (Figure 1). The model uses two event rates μ_1 and μ_2 , often referred to as first and second mutation rates, which lead from healthy target cells for lung cancer (N-cells) to initiated cells (I-cells) and malignant cells (M-cells). Initiated cells complete mitosis and produce two progeny cells at stochastic rate α and die or differentiate at stochastic rate β . Malignant cells develop into a detectable tumour mass (T) after a non-stochastic lag time (t_{lag}). In the current approach, radiation may influence μ_1 but not μ_2 . A repair–misrepair model is used to describe formation of simple (sl) and complex (cl) damage clusters by radiation and endogenous metabolic influences. Simple clusters include all classes of single strand breaks (SSBs) and multiply base damaged sites, and with complex clusters, we mean all classes of double strand breaks (DSBs). Let $L_i(t)$ denote the expected number of simple or complex clusters per cell at time t . Then, the rate of change in the expected number of simple or complex damage clusters per cell at time t may be written as

$$\frac{dL_i(t)}{dt} = P_i(t) - \lambda_i L_i(t) \quad (1)$$

where

$$P_i(t) = \begin{cases} P_i^{\text{endo}}, & -\infty < t \leq 0 \\ P_i^{\text{endo}}, & 0 < t \leq t_1 \\ P_i^{\text{endo}} + P_i^{\text{rad}}, & t_1 < t \leq t_1 + \Delta t \\ P_i^{\text{endo}}, & t > t_1 + \Delta t \end{cases} \quad (2)$$

with $i = sl, cl$. The term P_i stands for the expected number of i th type of damage cluster created by endogenous processes and radiation. It is $P_i^{\text{endo}} = \sum_i^{\text{endo}} \dot{D}_b$, $\dot{D}_b$ is the background dose rate (mGy/yr), and $P_i^{\text{rad}} = \sum_i^{\text{rad}} \dot{D}_x$, $\dot{D}_x$ is the dose rate from the exogenous radiation source and $\Delta t = D/\dot{D}_x$ (the irradiation time). $\sum_i^{\text{endo}}$ is the expected number of i th type (simple or complex) of lesions created by endogenous processes ($\text{cell}^{-1} \text{ year}^{-1}$), $\sum_i^{\text{rad}}$ is the expected number of i th type lesions created by radiation ($\text{mGy}^{-1} \text{ cell}^{-1}$) and λ_i (year^{-1}) is the rate of lesion removal (correct or incorrect repair). Values for these model parameters have been given (Schöllnberger et al., 2004). The values for λ_{sl} and λ_{cl} are $18,228 \text{ yr}^{-1}$ (repair half-time of 20 min) and $3,038 \text{ yr}^{-1}$ (repair half-time of 2 hr), respectively.

Equation (1) needs to be solved for four different time periods. The first is for $-\infty < t \leq 0$, with initial condition $L(t = -\infty) = 0$. The second time period is between birth and t_1 , when the person is artificially irradiated. Thereafter, a person receives dose D_x during time period Δt . For times $t > t_1 + \Delta t$, dose $D_x = 0$ again. The closed form solutions of this model are readily developed. The solution for $t > t_1 + \Delta t$, for example, is

$$L_i(t) = \frac{P_i^{\text{rad}}}{\lambda_i} (e^{\lambda_i \Delta t} - 1) e^{-\lambda_i(t-t_1)} + \frac{P_i^{\text{endo}}}{\lambda_i}. \quad (3)$$

The mutation rate at time t is

$$\frac{dM(t)}{dt} = \sum_i \frac{\varphi_i}{G(L_i)} \lambda_i L_i(t), \quad (4)$$

where φ_i is the probability that the i th type of lesion is misrepaired. The quantity $(1 - \varphi_i)$ is the probability that the i th type of lesion is repaired correctly. Here, $G(L_i)$ is a dimensionless scaling factor that accounts for radiologically induced adaptations in the accuracy of DNA damage repair. Values of $G(L_i)$ larger than one indicate enhanced repair accuracy, and values of $G(L_i)$ smaller than one indicate increased misrepair. On biophysical grounds, the quantity $\varphi_i/G(L_i)$ must be in the range $[0,1]$. In the model developed earlier (Schöllnberger et al., 2004; Schöllnberger et al., in press), a dose-rate-dependent Gaussian function was used for G . The applied Gaussian functions did not, however, allow simulation of repair induction by a dose as low as 1 mGy, as has been found by Broome et al. (2002) and Ulsh et al. (2004). It also seems to be more realistic to make the scaling function directly dependent on the amount of DNA damage in a cell, rather than the dose rate. We therefore introduce the following function that accounts for adaptations in DNA repair:

$$G(L) = 1 + \delta \left[1 - e^{-\gamma \Delta L(t)} \right]. \quad (5)$$

Here, δ is the maximum enhancement in DNA repair, and the term $e^{-\gamma \Delta L(t)}$ can be interpreted as the probability that a cell does not have a sufficient amount of DNA damage to trigger the adaptation. The larger the value is of γ , the faster G will reach the saturation value of $1 + \delta$, thereby reflecting the findings of Broome et al. (2002) and Ulsh et al. (2004). We have

$$\Delta L(t) = w_{sl} [L_{sl}(t) - L_{sl}(0)] + w_{cl} [L_{cl}(t) - L_{cl}(0)]. \quad (6)$$

Here, w_{sl} and w_{cl} are weights that can be used to adjust the relevant importance of each class of damage. The weights are normalised: $w_{sl} + w_{cl} = 1$. This concept allows the formulation of G in terms of simple or complex damage or both. This is important because the signal-to-noise level is high for DSBs and low for individual base damage and SSBs (i.e., radiation creates many DSBs compared to endogenous processes, whereas the converse is true for individual base damage and strand breaks).

Analogous to the previous studies (Schöllnberger et al., 2004; Schöllnberger et al., in press), we have

$$\mu_1(t) = \Omega \frac{dM(t)}{dt}. \quad (7)$$

Here, Ω is the probability that a mutation formed at a random location in the DNA induces genomic instability by modifying the expression or function of a critical gene. Therefore:

$$\mu_1(t) = \frac{\Omega}{G(L)} (\varphi_{sl} L_{sl}(t) \lambda_{sl} + \varphi_{cl} L_{cl}(t) \lambda_{cl}). \quad (8)$$

3 Results

Results are presented for $L_A(t) - L_A(0)$, after an artificial irradiation with dose $D_x = 100$ mGy at age 30. Two different irradiation times, Δt , were chosen: 1 day and 10 minutes. We investigate the case $w_{s,l} = 0$, which is especially interesting because of the high signal-to-noise ratio for DSB induction, as mentioned above. We found that the signal-to-noise ratio for clustered damage is about 10^5 , but only about 1.1 for simple damage clusters. These values have been calculated using the formulae $L_c(t)/L_c(0)$ and $L_s(t)/L_s(0)$ with $t = 30.000019$ years, i.e., at the end of the period of artificial irradiation which lasted $\Delta t = 10$ minutes. Similar values were obtained for $t = 30.0027$, i.e., at an age of 30 years + 1 day.

Figure 2A shows the predicted number of simple and complex lesions corrected for the lesions already present at birth, i.e., $t = 0$, as a function of dose. At age 30, the person has received a 90-mGy dose ($\dot{D}_b = 3$ mGy/yr). Soon after the artificial irradiation ended, $L_A(t)$ reverts back to the steady state level (not shown). Figure 2B shows the time-dependent increase in G at age 30 ($\delta = 3$, $\gamma = 0.5$). Figure 2C shows the change in μ_1 vs. dose for the case of no repair induction ($\delta = 0$, upper curve) and for $\delta = 3$ (lower curve). Analogous results are given in Figure 3 for the case of $\Delta t = 10$ minutes.

4 Discussion and conclusions

The earlier model approach (Schöllnberger et al., 2004; Schöllnberger et al., in press), which also focused on low-LET radiation, was limited to low dose rates. In areas of elevated background radiation, one can usually also find increased radon concentrations. Therefore, the previous studies are mostly limited to situations where workers receive an additional dose from γ -rays over an extended period of time, such as at nuclear power stations or nuclear fuel processing centres. In radiation accidents, however, a worker could be exposed to γ -radiation for a very short time only. In addition, the cell culture experiments of Azzam et al. (1996), Redpath and Antoniono (1998) and Redpath et al. (2001, 2003), for example, apply dose rates of a few mGy/min, which are many orders of magnitudes larger than the dose rates from environmental background radiation (mGy/yr). Therefore, a new model was needed that also considers endogenous DNA damage and possible protective effects from induced DNA repair and free radical scavenging.

The results presented here give typical shapes for the dose-dependence of induced simple and complex DNA damage clusters (Figures 2 and 3, panels A), for repair induction (panels B) and for mutation rates (panels C and D). Background radiation is considered (3 mGy/yr) together with an accidental short time radiation exposure to a low dose D_x of 100 mGy, delivered at two different dose rates $\dot{D}_x$. Panels A in Figures 2 and 3 show that radiation produces many more simple than complex clusters. Endogenous processes produce practically no complex clusters ($L_c(0) = 4 \times 10^{-5}$ versus $L_s(0) = 3846$). Therefore, the signal-to-noise ratio is much higher for clustered than simple damage (i.e., $L_c(t)/L_c(0) \gg L_s(t)/L_s(0)$). The protective effects of low dose radiation exposure are reflected in decreased values of μ_1 , as shown in Figures 2 and 3 (lower curves in panels C and D). The amount of the decrease in μ_1 reflects the values for $G(L)$, as given in panels B of Figures 2 and 3. Panels D give the time dependence of μ_1 .

In summary, the model makes predictions about how induced DNA repair reduces mutation rates after low dose, high dose-rate irradiation. Future studies will include radical scavenger induction and will integrate the mutation model into the two-stage cancer model for risk predictions.

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Biographical notes

Helmut Schöllnberger obtained his Masters degree and PhD at Technical University Vienna between 1985 and 1996. He carried out postdoctoral research from 1997 to 1999 at UNC Chapel Hill, Institute for Environmental Studies, and continued his postdoctoral research from 1999 to 2001 at Lovelace Respiratory Research Institute. He was a guest professor at the University of Salzburg from 2001 to 2002, then until 2004 he was EU Marie Curie Individual Fellow at the National Institute for Public Health and the Environment (RIVM), The Netherlands. He is now with the University of Salzburg.

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Figure 1. Conceptual view of the two-stage model with clonal expansion. See Section 2 for an explanation of the symbols

Figure 2.

Predicted number of simple and complex lesions as a function of dose, corrected for the lesions already present at birth (panel A); time-dependent increase in G at age 30 ($\delta = 3$, $\gamma = 0.5$) (panel B); mutation rate, μ_1 , plotted vs. dose for the case of no repair induction ($\delta = 0$, upper curve) and for repair induction with $\delta = 3$ (lower curve) (panel C); mutation rate, μ_1 , plotted vs. age for the case of no repair induction ($\delta = 0$, upper curve) and for $\delta = 3$ (lower curve) (panel D). Here, the duration of the artificial short time irradiation with dose $D_X = 100$ mGy was taken to be 1 day ($\Delta t = 1$ day)

Figure 3.
Analogous results as in Figure 2 for $\Delta t = 10$ minutes