An examination of radiation hormesis mechanisms using a multi-stage carcinogenesis model

Introduction

Tumour-reducing, bio-positive effects of low doses of ionising radiation have been discussed in a controversial manner for many decades. Feenendegen, Pollycove and colleagues have proposed several concepts that may give rise to hormesis effects. One key aspect of their hormesis concept is based on the idea that the radiologically induction of cellular defence mechanisms, such as DNA repair and radical scavenging, may reduce the harmful effects of endogenous DNA damage. We have used a multi-stage cancer model to conduct a series of sensitivity studies. The results of these sensitivity studies have been used to help identify critical model inputs and to help define the shapes of the cumulative lung cancer incidence curves that may arise when dose and dose rate dependent cellular defense mechanisms are incorporated into a multi-stage cancer model.

Methods

The model comprises the main stages of carcinogenesis: initiation, clonal expansion of initiated cells, malignant transformation and a lag time, t0, of tumour formation. Rate constant k describes the induction of genomic instability in State 0 and State 1

\[ k = \Omega \sum \left( \sum_{i} \left( \sum_{j} D_{i} \right) \right) \]

\[ \sum_{k} \text{expected number of } k \text{ type (simple or complex) lesion created by endogenous processes (cell)}^{-1} \text{ year}^{-1} \]

\[ \sum_{j} \text{expected number of } j \text{ type lesion created by radiation (mGy)}^{-1} \text{ cell}^{-1} \]

\[ D_{i} \text{ dose rate (mGy) year}^{-1} \]

\[ \phi_{j} \text{ probability that a mutation formed at a random location in the DNA is misrepaired} \]

\[ \Omega \text{ probability that a mutation formed at a random location in the DNA induces genomic instability by modifying the expression or function of a critical gene} \]

Rate constant krad was assumed to be independent of dose and dose rate.

To incorporate adaptive protection into the model, k is rewritten as

\[ k = \Omega \sum_{k} \sum_{j} \left( \sum_{i} \left( \sum_{D_{i}} F(D_{i}) \right) \right) \]

\[ F(D_{i}) = A_{i} b_{i} \exp \left( -c_{i} \right) \]

\[ G(D_{i}) = A_{i} b_{i} \exp \left( -c_{i} \right) \]

\[ G_{j}(D_{i}) \text{ and } F_{j}(D_{i}) \text{ account for changes in the } \phi_{j} \text{ as a function of dose rate and for changes in the radical scavenging capacity of a cell, respectively. } D_{i} = D_{i} = 2.67 \text{ mGy year}^{-1} \]

The background dose rate in the U.S. \( A_{i}, B_{i}, C_{i}, D_{i}, E_{i}, F_{i} \) are adjustable parameters. Their values were gained by producing functions as given in Figure 2.

To obtain estimates for \( \phi_{j} \), other model inputs were set a priori to the best estimate values gained from the literature. Then, \( \Omega \) was adjusted so that the cumulative lung cancer incidence rate for the 75 mGy and 1 Gy were consistent with the values reported by the ICRP.

Results

Figure 3 shows the model-predicted cumulative lung-cancer incidence level with and without the endogenous DNA damage terms (i.e., \( \sum_{k} \text{ and } \sum_{j} \text{ terms} \)). Figure 4 illustrates the effects that radiation-induced adaptations in DNA repair (left panel) and radical scavenging (right panel) may have on the cumulative incidence of lung cancer. For all of the studies shown in Figure 4, F and G reach a maximum at 200 mGy (i.e., the dose that corresponds to \( D_{i} = 2.67 \text{ mGy year}^{-1} \)). Figure 5 shows the combined effects of cellular adaptations in radical scavenging and DNA repair processes.

Conclusions

- For dose levels comparable to background radiation, endogenous DNA damage may account for 70 - 90% of the predicted cancers. For a lifetime dose of 1 Gy, endogenous processes may account for as much as 30% of the predicted cancers.
- These predictions are sensitive to the rate at which double strand breaks and other multiply damaged sites are created by endogenous processes \( \sum_{k} \text{ term} \).
- Additional research is required to determine if and to what extent endogenous processes can create complex DNA damage.
- In the model described, U-shaped curves are only produced when both the accuracy of DNA repair and the capacity for radical scavenging are enhanced 3 fold.

Acknowledgements

Work partially supported by the EU project CEC Contract FIGH-CT-1999-00005, by a Marie Curie Individual Fellowship EC Contract No FIGH-CT-2002-50513 and by the Low Dose

Rivm Research Program, Biological and Environmental Research (BIR), U.S. Department of Energy, Grant No. DE-FG02-03BER3541.

P.O. Box 1, 3720 BA Bilthoven, the Netherlands
www.rivm.nl

H. Schöllnberger, R.D. Stewart, R.E.J. Mitchell, W. Hofmann

RIVM, Bilthoven, The Netherlands
Purdue University School of Health Sciences, West Lafayette, Indiana, USA
Atomic Energy of Canada Limited Chalk River Laboratories, Chalk River, Canada
Institute of Physics and Biophysics, University of Salzburg, Austria