Effects of Intercellular Signal-Mediated Cell Death and Neoplastic Transformation on Transformation Frequency at Low Doses of Ionizing Radiation

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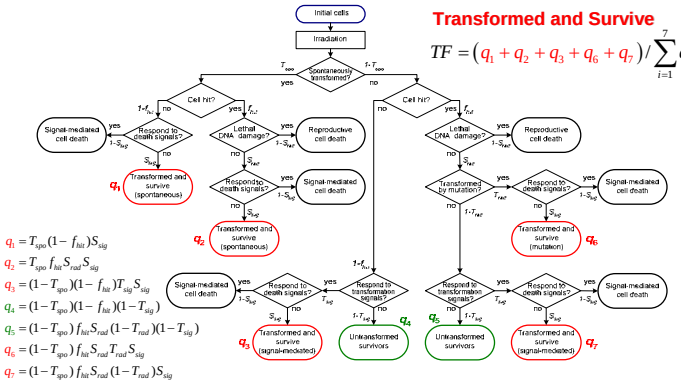
Introduction

A series of models describing neoplastic transformation frequency as a function of absorbed dose is presented. Model components, such as the fraction of cells directly hit by radiation, the fraction of cells surviving intercellular death signals and the fraction of cells transformed by intercellular signals, are derived using a microdosimetric approach. The models are premised on the idea that cell death and neoplastic transformation can be initiated by signal-mediated processes as well as direct radiation damage. A model that assumes that only those cells destined to become transformed are sensitive to intercellular death signals is consistent with data from several microbeam and broad beam experiments. The model predicts that, for cells exhibiting high levels of signal-mediated death and low levels of signal-mediated transformation, a suppression of transformation below the spontaneous level may occur for low doses, as has been observed in some experiments performed using low-LET radiation. However when the balance of signal-mediated cell death and signal-mediated neoplastic transformation is reversed, the model predicts that the response to low doses of low-LET radiation becomes supra-linear with no evidence for suppression of spontaneous neoplastic transformation. The suppression effect also vanishes if cells are assumed to be irradiated by high-LET radiation instead of low-LET radiation and when the spontaneous transformation frequency is small. The latter result suggests that, in cells that do not exhibit elevated levels of spontaneous transformation, low radiation doses produce no suppression of spontaneous transformation and even the lowest doses are expected to cause increased cell transformation.

Methods

The proposed model for cell transformation is premised on the idea that cell death and neoplastic transformation can be initiated by signal-mediated processes as well as direct radiation damage. Three cell-signaling scenarios are considered: (1) signal-mediated cell death is absent (fully suppressed), (2) signal-mediated death may act on all cells regardless of their damage state, and (3) signal-mediated death only acts on transformed cells or cells destined to become transformed. In addition, two scenarios in which signal-mediated neoplastic transformation is either absent or present are considered. These scenarios result in six possible models. As an example, flowchart for a model in which signal-mediated cell death and neoplastic transformation are present and only transformed cells are sensitive to intercellular death signals is shown.



The microdosimetric approach of Stewart *et al.* (2006) to relate absorbed dose to the emission and processing of cell death signals by unirradiated cells is adopted and extended to describe signal-mediated cell transformation processes. Expression for transformation frequency per surviving cell corresponding to the flowchart is shown to the right for broad beam and microbeam irradiation protocols.

Broad Beam Irradiation

$$T_{spo} = \text{constant}$$
$$f_{hit} = 1 - e^{-D/\overline{z}_F}$$
$$S_{rad} = \exp\left[-\alpha D - \beta D^2\right]$$
$$S_{sig} = \exp\left[-\omega_S\left(1 - e^{-D/\overline{z}_F}\right)\right]$$
$$T_{rad} = 1 - e^{-\gamma D}$$
$$T_{sig} = 1 - \exp\left[-\omega_T\left(1 - e^{-D/\overline{z}_F}\right)\right]$$

Microbeam Irradiation

$$T_{spo} = \text{constant}$$
$$f_{hit} = \{\text{Hit cells}\}/\{\text{All cells}\}$$
$$S_{rad} = \exp\left[-\alpha \overline{z}_F n - \beta\left(\overline{z}_F n\right)^2\right]$$
$$S_{sig} = \exp\left[-\omega_S\left(1 - e^{-n}\right)\right]$$
$$T_{rad} = 1 - e^{-\gamma \overline{z}_F n}$$
$$T_{sig} = 1 - \exp\left[-\omega_T\left(1 - e^{-n}\right)\right]$$

Results

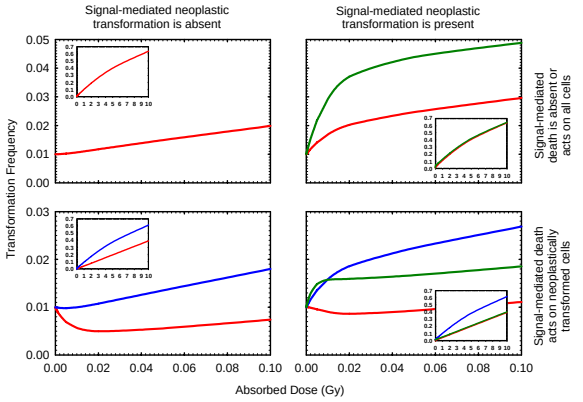


Figure 1. Transformation frequency at low radiation doses (0–0.1 Gy) for different scenarios of signal-mediated cell death and transformation. Parameter values are as follows: red curve – $T_{spo} = 0.01$, $\overline{z}_F = 0.01$, $\alpha = 0.1\ \text{Gy}^{-1}$, $\beta = 0.01\ \text{Gy}^{-2}$, $\omega_S = 1$, $\gamma = 0.1\ \text{Gy}^{-1}$, $\omega_T = 0.01$; blue curve – $\omega_S = 0.1$ (all other parameters are the same as for the red curve); green curve – $\omega_T = 0.03$ (all other parameters are the same as for the red curve). Inserts show behavior of transformation frequency at higher doses (0–10 Gy). The assumptions that signal-mediated cell death is absent or that it acts equally on all transformed and untransformed cells result in the same expressions for transformation frequency per surviving cell.

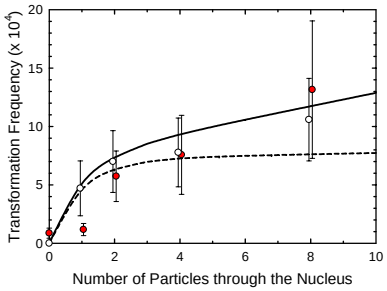


Figure 2. Neoplastic transformation of C3H 10T½ cells after microbeam irradiation with 5.3 MeV α particles. Measured data are from Sawant *et al.* (2001). Filled red circles and solid line: 100% of cell nuclei were exposed to exact number of α particles. Open circles and dashed line: 10% of cell nuclei were exposed to exact number of α particles. Model parameters are:

$$\gamma = 1.33\times10^{-2}\,\text{Gy}^{-1},\ \omega_S = 0,\ \omega_T = 7.16\times10^{-4}$$
$$\overline{z}_F = 4.3\ \text{mGy},\ S_{rad} = 1,\ T_{spo} = 0$$

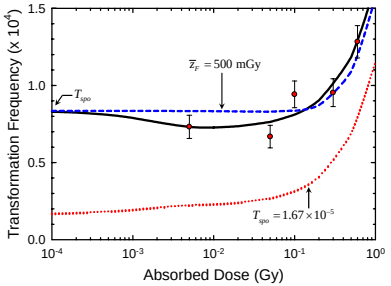


Figure 3. Neoplastic transformation of HeLa × skin fibroblast human hybrid CGL1 cells. Filled red circles: measured data for 232 MeV protons (Elmore *et al.* 2005). Solid black lines: fit to measured data. Red dotted line: T_{spo} reduced 5-fold from 8.35×10^{-5} to 1.67×10^{-5}. Blue dashed line: $\overline{z}_F$ increased from 2 mGy to 500 mGy. Except where explicitly noted otherwise, parameters are:

$$\gamma = 1.26\times10^{-4}\,\text{Gy}^{-1},\ \omega_S = 0.3,\ \omega_T = 1.33\times10^{-5}$$
$$\overline{z}_F = 2\ \text{mGy},\ S_{rad} = 1,\ T_{spo} = 8.35\times10^{-5}$$

Conclusions

- Although damaged and undamaged cells may potentially undergo signal-mediated death or neoplastic transformation, ***only*** the model that assumes signal-mediated transformation is present and restricts signal-mediated death to transformed cells (or cells destined to become transformed) is able to predict ***both*** the *U-shaped responses* observed in low LET studies (e.g., Elmore *et al.* 2005) and the *supra-linear* responses observed in high-LET studies (e.g., Sawant *et al.* 2001)
- Proposed model successfully reproduces dose-response relationships observed in microbeam (**Figure 2**) and broad beam (**Figure 3**) studies
- Model predicts that suppression of transformation frequency below the spontaneous level vanishes when cells are irradiated with high-LET radiation instead of low-LET radiation (**Figure 3, blue dashed line**)
- Model also predicts that the suppression of spontaneous transformation is replaced by a linear or supra-linear dose-response relationship as the spontaneous transformation rate decreases (**Figure 3 dotted line**)
  - Suggests that, in the majority of human cells exhibiting very low levels of spontaneous transformation, no suppression of transformation frequency by low doses of radiation occurs – the lowest possible doses of radiation may increase the transformation of normal human cells

References

- E. Elmore, X-Y. Lao, M. Ko, S. Rightnar, G. Nelson and J. L. Redpath, Neoplastic transformation *in vitro* induced by low doses of 232 MeV protons. *Int. J. Radiat. Biol.* **81**, 291–297 (2005).
- S. G. Sawant, G. Randers-Pehrson, C. R. Geard, D. J. Brenner and E. J. Hall, The bystander effect in radiation oncogenesis: I. Transformation in C3H 10T½ cells *in vitro* can be initiated in the unirradiated neighbors of irradiated cells. *Radiat. Res.* **155**, 397–401 (2001).
- R. D. Stewart, R. K. Ratnayake and K. Jennings, Microdosimetric model for the induction of cell killing through medium-borne signals. *Radiat. Res.* **165**, 460–469 (2006).

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