Modeling Bystander Effects Using a Microdosimetric Approach

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Introduction

Mechanistic models are needed to help guide, interpret, and quantify the results of microbeam and low-dose experiments. Although there is increasing evidence that bystander effects play a role in low dose radiation responses, few models have been developed to account for these phenomena. A new radiobiological model proposed by us accounts for the possibility that cellular responses arise as the result of both radiation damage and the reception and processing of intercellular signaling.

Concepts from microdosimetry are used to partition the irradiated cell population into two groups: (1) the response of the ***severely damaged cells*** is determined by the radiation damage alone (the classic radiobiologic paradigm); severely damaged cells are unresponsive to intercellular signals that modulate apoptosis and cell transformation and (2) ***weakly damaged cells*** comprised of cells that are not damaged by radiation (i.e., bystanders) and by cells that sustain a non-critical level of radiation damage (termed here the walking wounded). The response of the weakly damaged cells (bystanders and walking wounded) is determined both by the radiation damage and by events triggered through cell-to-cell communication. The collective response of the entire cell population is the sum of the responses of the weakly and severely damaged cells.

Formulation of Response Models

The collective response of the weakly and severely damaged cells is given by

$$R(D) = pB(D_w) + (1-p)H(D_s)$$

where B is the response function for the weakly damaged cells and H is the response function for the severely damaged cells. D_w and D_s are the delivered doses to the weakly and severely damaged cells, respectively.

Response Models for Severely Damaged Cells

$$H_S(D_s) = \exp\left[-D_s(a + b\,D_s)\right] \quad \text{Survival}$$

$$H_{neo}(D_s) = g\,D_s \quad \text{Neoplastic transformation per survivor}$$

Response Models for Weakly Damaged Cells

$$B_S(D_w) = \frac{\exp\left[-D_w(a + b\,D_w)\right]}{1 + m_{apop}\,p_{apop}^{signal}\left[g\,D_w + m_{neo}\,p_{neo}^{signal}(1 - g\,D_w)\right]}$$

$$B_{neo}(D_w) = (1 - m_{apop}\,p_{apop}^{signal})\left[g\,D_w + m_{neo}\,p_{neo}^{signal}(1 - g\,D_w)\right]$$

Results

In the absence of apoptosis ($m_{apop} = 0$), the parameters listed below are equivalent to those reported by Brenner *et al.* (2001):

$a = 2.243\ \text{Gy}^{-1}$ $\quad b = 1.522\ \text{Gy}^{-2}$

$g = 1.570\times10^{-3}\ \text{Gy}^{-1}$

$m_{neo} = 6.4\times10^{-4}$

$\overline{z}_F = 0.074\ \text{Gy}$

57.5% of transformed cells receiving an apoptosis signal undergo apoptosis

$m_{apop} = 0.575$

Dosimetry

A Poisson distribution with expectation value v adequately describes the distribution of the number of radiation events experienced among cells in a region of interest (ROI)

$$D = \sum_{n=0}^{\infty}(n\overline{z}_F)\,p(n\,|\,v) = \overline{z}_F\sum_{n=0}^{\infty}np(n\,|\,v) = v\overline{z}_F$$

The probability p a randomly selected cell in the ROI experiences fewer than N hits is

$$p = \sum_{n=0}^{N-1}p(n\,|\,v) = e^{-v}\sum_{n=0}^{N-1}\frac{v^n}{n!}$$

The delivered dose to the entire cell population is related to the delivered dose to the weakly and severely damaged cells as

$$D = pD_w + (1-p)D_s$$

where

$$D_w \equiv \frac{\overline{z}_F}{p}\sum_{n=0}^{N-1}np(n\,|\,v) \qquad D_s \equiv \frac{\overline{z}_F}{(1-p)}\sum_{n=N}^{\infty}np(n\,|\,v) = \frac{D - pD_w}{1-p}$$

Signaling Models

$$p_{neo}^{signal} = 1 - \left\{e^{-(D/\overline{z}_F)}\sum_{n=0}^{M-1}\frac{(D/\overline{z}_F)^n}{n!}\right\}^{N_c}$$

Damaged cells send a neoplastic transformation signal to N_c nearby cells.

$$p_{apop}^{signal} = 1 - \left\{e^{-(D/\overline{z}_F)}\sum_{n=0}^{M-1}\frac{(D/\overline{z}_F)^n}{n!}\right\}^{6}$$

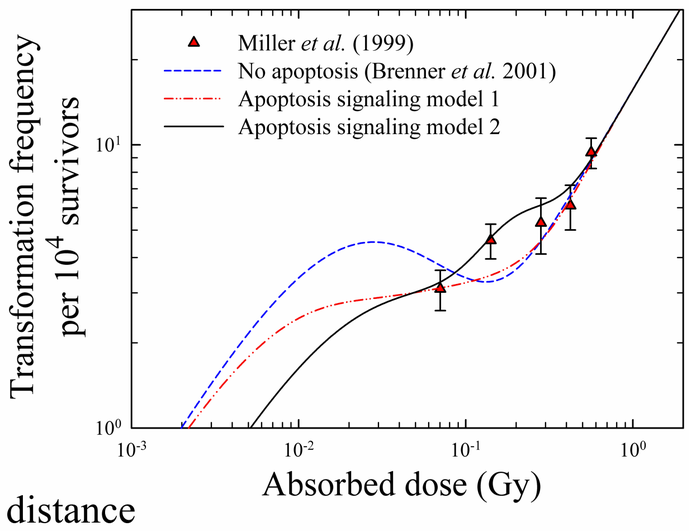
Model 1. Damaged cells emit signals that stimulate apoptosis in 6 nearby cells.

$$p_{apop}^{signal} = 1 - \left\{1 - e^{-(D/\overline{z}_F)}\sum_{n=0}^{M-1}\frac{(D/\overline{z}_F)^n}{n!}\right\}^{7}$$

Model 2. Cells emit signals that suppress apoptosis until they sustain a critical level of radiation damage.

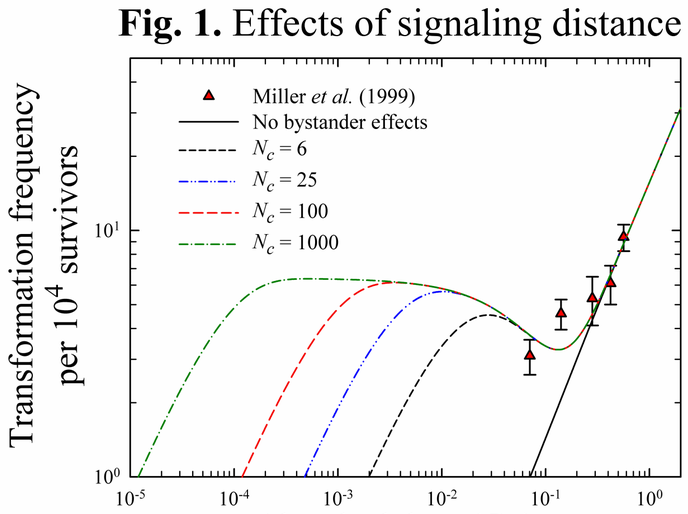
- **Model 1**: fraction of the weakly damaged cells receiving an apoptosis signal *increases* as the dose of radiation *increases*.
- **Model 2**: fraction of the weakly damaged cells receiving an apoptosis signal *increases* as the dose of radiation *decreases*.

Fig. 2. Effects of apoptosis



- **Best fits to the Miller *et al.* (1999) data are obtained with the model that includes the selective removal of transformed cells through apoptosis.**
- **Cells emit signals that suppress apoptosis until they sustain a critical level of damage (i.e., signaling model 2 gives a better fit than model 1).**

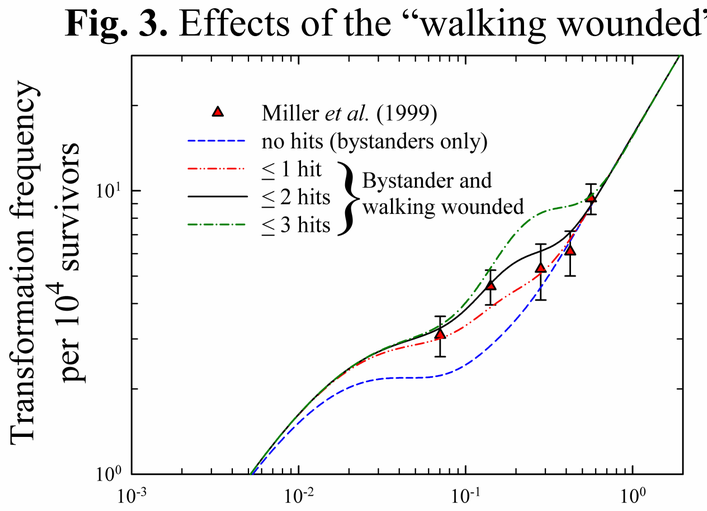
Fig. 1. Effects of signaling distance



Cells that sustain 1 or 2 radiation hits still respond to intercellular signals governing apoptosis and neoplastic cell transformation.

The width of the low-dose plateau increases rapidly as the signaling distance (N_c) increases (no apoptosis).

Fig. 3. Effects of the "walking wounded"



Conclusions

- Signal transmission distance (Fig. 1) and directionality (signaling model 1 vs. model 2) are two important aspects of the bystander model.
- Apoptosis selectively removes a portion of the transformed cells (Fig. 2).
- Cells emit signals that tend to suppress apoptosis until they sustain some critical level of damage (Fig. 2).
- Selective removal of transformed cells through apoptosis is more effective for small doses than for large doses (Fig. 2).
- Both the radiation damaged ("walking wounded") and undamaged (bystander) cells respond to intercellular signals that govern apoptosis and cell transformation (Fig. 3).

References

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