Implications of intercellular signaling for the shapes of dose-response relationships

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Purpose: Although microbeam and medium transfer experiments provide compelling evidence that cells damaged by radiation transmit signals to nearby bystander cells (reviewed in Hall 2003), the implications of these phenomena for the shapes of dose-response curves after low and moderate doses of radiation are largely unknown. The transition from high to low dose involves qualitative and quantitative differences in the spatial pattern of energy deposited among cells. For large doses, all of the cells in the tissue (or Petri dish) are hit many times. For moderate doses, some cells are hit many times and other cells are only hit once or not at all. For lower doses of radiation, very few cells are hit more than one time and the ratio of the number of bystanders (non-hit) to radiation-damaged (hit) cells increases as the absorbed dose decreases.

To gain insight into the potential impact of intercellular signaling for the shapes of dose-response relationships, we formulated probabilistic models, based on microdosimetric principles, to simulate intercellular communication and signal transduction initiated by the uniform irradiation of a multicellular system. The shapes of dose-response curves that arise as a result of alternate signaling models are examined. The hypothesis that bystander and radiation-damaged cells may respond in quite different ways to the same intercellular signals is considered. An example illustrating the application of the signaling models to the analysis of data from a medium transfer experiments is presented.

Intercellular Signaling Models: Two types of signaling mechanism are considered: (1) *broadcast signaling* and (2) *feedback signaling*. In the broadcast signaling model, cells damaged by radiation emit stress-related signals. In the feedback signaling model, the initial signal generated by the radiation-damaged cells triggers the release of secondary (feedback) signals by undamaged (bystander) cells and/or damaged cells. **Figure 1** shows examples of the model predicted trends for high-LET radiation. **Figure 2** shows examples of the trends in the time-integrated signal intensity after a uniform dose of low- or high-LET radiation. The initial signal "broadcast" by the hit cells reaches a plateau near the frequency mean specific energy and then starts to increase again as the number of cells hit multiple times continues to increase. The intensity of the broadcast signal approaches zero for small doses because the probability that at least one cell in the system is hit by radiation decreases as the absorbed dose decreases. Feedback signals generated by the bystander cells reach a maximum when the absorbed dose equals 0.693 (=ln2) times the frequency-mean specific energy. For higher doses, the intensity of the feedback signal decreases as dose increases because the number of bystander cells decreases as absorbed dose increases. The peak in the signal shifts to higher doses if cells hit 1 to *m* times ("bruised cells") also generate secondary signals in response to the initial radiation-induced signal.

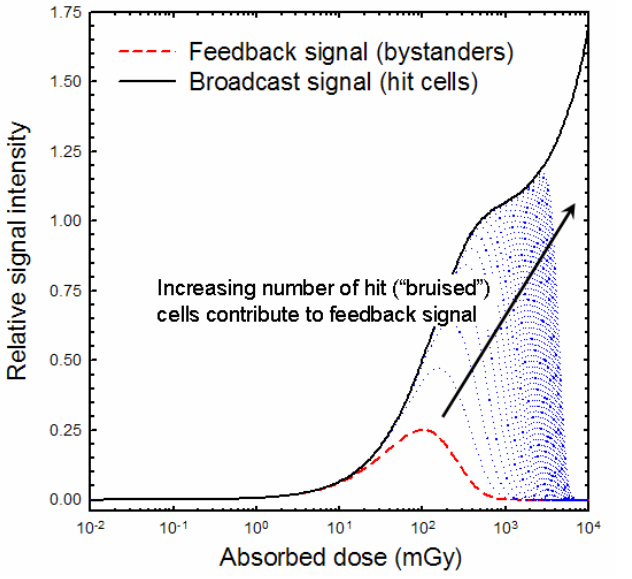

Figure 1. Time-integrated signal intensity generated in a multicellular system after uniform irradiation. Blue dotted lines show the effects of including feedback signals generated by cells hit $\leq m$ time (1 to 30 hits), i.e., the *bruised cells*.

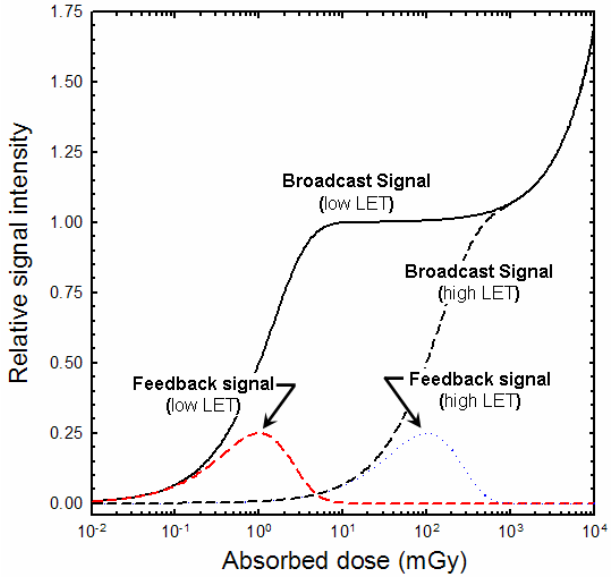

Figure 2. Time-integrated signal intensity generated in a multicellular system after uniform irradiation by low- and high LET radiation. Peaks in the feedback signal generated by the bystander cells occur at $0.693\,\overline{z}_F$ (1 and 100 mGy).

Medium Transfer Experiment: Figure 3 shows a comparison of the fraction of the HPV-G recipient cells that survive following treatment by culture medium harvested from cells irradiated with doses from 5-5000 mGy. The surviving fraction was computed using the formula

$$S = \exp\{-\alpha I_S(D)\},$$

where I_S is the intensity of the bystander signal as a function of the donor dose D and α is the probability per unit signal strength that a cell is lethally damaged as a result of the bystander signal. For a donor dose of 5 mGy, the average number of hits per cell is ~ 25, which suggests that all of the donor cells contribute to the bystander signal. For doses below ~ 1 mGy, the intensity of the bystander signal decreases because an increasingly large fraction of the donor cells are not hit by radiation.

Acknowledgements

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References

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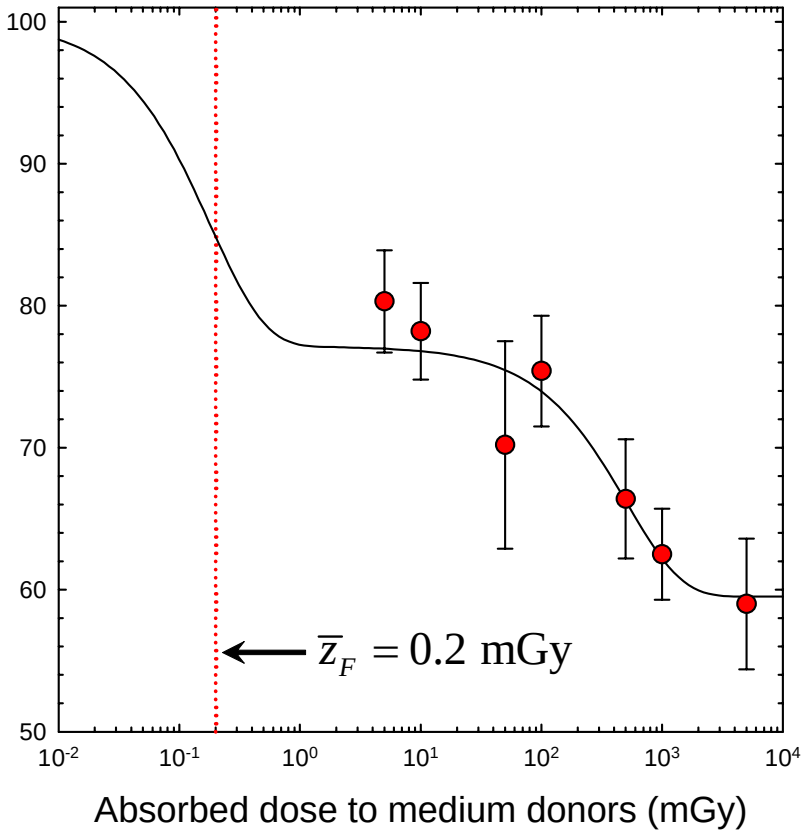

Figure 3. Survival of HPV-G cells following treatment by culture medium harvested 1 hour after uniform irradiation of 10^5 cells by ^{60}Co γ-rays. **Filled symbols:** measured data from Table 1 in Mothersill and Seymour (2002). **Solid line:** bystander signal simulated using the broadcast model.