Biologic Responses to Low Doses of Ionizing Radiation: Adaptive Response Versus Bystander Effect

TO THE EDITOR: In their Newsline commentary, Drs. Feinendegen and Pollycove call an important issue to the attention of readers of *The Journal of Nuclear Medicine* (*1*). In a discussion of the dual action of ionizing radiation, they posit a competition at low doses between the direct induction of radiation damage and the activation of damage control (adaptive response, hormesis), such that below 0.2 Gy the frequency of oncogenic transformation is lower than background and net radiation damage does not approximate the linear extrapolation model until ~0.5 Gy (Fig. 10 of Feinendegen and Pollycove).

In their text, Feinendegen and Pollycove (*1*) state that bystander cells (unirradiated neighbors of irradiated cells that are influenced by the latter) may respond similarly to those hit directly by radiation; indeed, there is evidence for this phenomenon (*2*). However, there is a robust literature, which the authors fail to mention, that suggests the bystander effect amplifies the consequences of irradiation rather than blunting them.

Brenner et al. (*3*) propose a contrary model of the low-dose bystander effect. Their Figure 4 is the obverse of Figure 10 of Feinendegen and Pollycove (*1*). Accordingly, the induced rate of oncogenesis is greater (not less) than the linear extrapolation at doses below 0.4 Gy (40 cGy).

In an attempt to explore the apparent competition between the adaptive response and the bystander effect, Sawant et al. have examined the results from irradiation of cells with α-particle beams (*4*). When cell survival is the endpoint, a pronounced bystander effect, decreasing survival below that produced by direct irradiation alone, is reduced ~50% on preirradiation with 2 cGy γ-photons as an adaptive stimulus. With radiation-induced transformation as the endpoint, an adaptive stimulus lessening a positive bystander effect could not be clearly demonstrated.

All of this suggests that we are still ignorant of what really happens at low doses and that the case cannot be made facilely for responses either below or above the linear extrapolation.

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REPLY: In his letter to the editor about our article (*1*), Dr. Adelstein lists several concerns that also appear repeatedly in other discussions on the role of adaptive or protective responses. Dr. Adelstein states that we failed to mention robust literature that suggests that the bystander effect amplifies the consequences of irradiation rather than blunting them. On page 21N of our article, we clearly point to the bystander effect as a source of DNA damage in nonirradiated cells that are neighbors to irradiated cells. This is, indeed, well known. However, if one deals with data that are stochastically generated and summarily measured in multicellular systems, one should be careful in generalizing the statement that the bystander effect amplifies the consequences of irradiation. Our article and other analyses examine all-inclusive responses of cell populations and tissues at low doses; here, protective responses readily appear at low doses of low–linear energy transfer (LET) radiation, where damaging effects are hardly or not at all measurable. Radiation effects in cell populations and tissues are always the consequence of any and all cell responses in the system. Bystander effects are, of course, included in the ensuing results.

Dr. Adelstein cites the paper by Brenner et al. (*2*) as contradicting our graphic display of the potential consequences of the dual effect of radiation on DNA at low doses, as expressed in Figure 10 in our article (*1*). Yet, the 2 sets of data cannot be compared, because Brenner et al. focus on radiation-induced damage and exclude potential protective responses in their experiments. Regarding the latter, 2 issues need attention: One concerns direct responses and the other those via the bystander effect.

Regarding the direct cellular protective responses, Dr. Adelstein overlooks our Figure 9 (*1*), which clearly summarizes, schematically, the protective responses to have a maximum at low doses of low-LET radiation and disappear at high doses. At equal low tissue doses, cell doses of low-LET radiation are low, whereas cell doses of high-LET radiation are high. The article by Brenner et al. (*2*) reports on cell-targeted α-particle irradiation (5.3 MeV), resulting in a mean dose to the mass of individual cells in the range of 300 mGy per particle track. As summarized in Figure 9 of our article, the high-dosed cells themselves are unlikely to express a protective response other than apoptosis.

Regarding protective responses via the bystander effect, Dr. Adelstein disregards the fact that protective responses generally develop with a time delay of hours after single irradiation, as is well outlined in our article. In their experiments, Brenner et al. (*2*) trypsin-treated the α-particle–irradiated cells right after exposure and plated them at a low density of about 300 viable cells per dish, according to a relevant technical article (*3*). From all that we know, trypsin treatment causes considerable cell stress. Changing the cellular milieu soon after radiation exposure practically excludes the development of protective responses (*4*). For a protective response to develop after irradiation, a time delay of hours without cell perturbation is needed. This need is widely recognized and has been clearly evident, such as in experiments reported by Azzam et al. (*5*), in which clonogenic cell transformation in culture cells was significantly reduced after a single low-dose low-LET irradiation. Accordingly, the model presented by Brenner et al. does not allow a reference to protective responses.

In addition, the article on modeling by Brenner et al. (*2*) omits any control values. These are, however, included in the preceding technical article by Sawant et al. (*3*). Also, the data from repeated experiments that are given in the technical article do not appear in

the crucial dataset in the modeling paper, because, as the authors state in the technical article, ". . . two repeats of the part of the experiment in which 10% of the cells were exposed to exactly one alpha-particle. . . did not produce such enhanced effects, although no internal controls were assessed for these repeats." Again, this indicates the intent of the modeling article by Brenner et al. to indeed focus uniquely on the damaging bystander effect after low doses of high-LET radiation.

In referring to a subsequent article by Sawant et al. (*6*), Dr. Adelstein rightly acknowledges the protective response of a conditioning dose of 2 cGy on the damaging bystander effect on cell survival, when the 2 cGy were given 6 h before exposure to the challenging α-particles. As Dr. Adelstein also correctly indicates, the protective effect on cell transformation in these experiments with α-particles was borderline significant in that the fraction of dishes with transformed foci was 0.31 ± 0.03 in controls and 0.26 ± 0.03 after the conditioning dose of 2 cGy. However, the cells were trypsin-treated and plated right after the challenging α-irradiation. Cell stress from trypsin treatment right after irradiation likely interferes with the mechanisms for protective responses to affect cell transformation and must be experimentally excluded in such studies.

In referring to the article by Matsumoto et al. (*7*), Dr. Adelstein principally concurs that protective responses in nonirradiated cells are induced by bystander effects after low-dose low-LET irradiation. Whether such a protective bystander effect also operates after low doses and dose rates of high-LET radiation remains a challenging and crucial question. Experimental evidence in the literature, however, supports a positive answer.

Thus, Dr. Adelstein's comments do not at all contradict our article, and they are, in part, irrelevant. Nevertheless, the low-dose specific phenomenon of protective responses in cell populations and tissues, as we now know, directly bears on our approach to relate health risks to low doses of ionizing radiation. Despite the clear need for much more work, protective responses at low doses contradict the validity of the linear-no-threshold hypothesis and should not be disregarded in future attempts at arriving at reasonable and justified radiation protection recommendations. It is good to agree with Dr. Adelstein that low-dose radiobiology, particularly at the cellular level, is indeed a great challenge.

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