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The Impact of Adaptive and Non-targeted Effects in the Biological Responses to Low Dose/Low Fluence Ionizing-Radiation: The Modulating Effect of Linear Energy Transfer

Sonia M. de Toledo[*], **Manuela Buonanno**[*], **Min Li**[*], **Nesrin Asaad**[*], **Yong Qin**[*], **Jie Zhang**[*], and **Edouard I. Azzam**[*]

[*]Department of Radiology, UMDNJ-New Jersey Medical School Cancer Center, 205 South Orange Avenue, Newark, NJ 07103, USA

Abstract

A large volume of laboratory and human epidemiological studies have shown that high doses of ionizing radiation engender significant health risks. In contrast, the health risks of low level radiation remain ambiguous and have been the subject of intense debate. To reduce the uncertainty in evaluating these risks, research advances in cellular and molecular biology are being used to characterize the biological effects of low dose radiation exposures and their underlying mechanisms. Radiation type, dose rate, genetic susceptibility, cellular redox environment, stage of cell growth, level of biological organization and environmental parameters are among the factors that modulate interactions among signaling processes that determine short- and long-term outcomes of low dose exposures. Whereas, recommended radiation protection guidelines assume a linear dose-response relationship in estimating radiation cancer risk, *in vitro* and *in vivo* investigations of phenomena such as adaptive responses and non-targeted effects, namely bystander effects and genomic instability, suggest that low dose/low fluence-induced signaling events act to alter linearity of the dose-response relation as supported by the biophysical argument. The latter predicts that increases in dose simply increase the probability that a given cell in a tissue will be intersected by an electron track, and by corollary, each unit of radiation, no matter how small would increases risk. These predictions assume that similar molecular events mediate both low and high dose radiobiological effects, and the cumulative risk from two sequential radiation exposures can never be less than one alone.

Keywords

Low dose; adaptive response; LET; Dose-rate

Using normal human or rodent cells maintained in culture and a variety of biological endpoints, studies have shown that exposure to low dose/low linear energy transfer (LET) radiation delivered at low dose-rates (≤ 10 cGy from ^{137}Cs or ^{60}Co γ rays delivered at ≤ 0.2 cGy/h), triggers signaling events that protect cells from endogenous oxidative damage or damage due to a subsequent challenge dose of ionizing radiation (Azzam et al. 1994, Azzam

For correspondence or reprints, contact Edouard I. Azzam, Department of Radiology, UMDNJ-New Jersey Medical School Cancer Center, 205 South Orange Avenue, Newark, NJ 07103, USA or azzamei@umdnj.edu.

et al. 1994, Azzam et al. 1996, de Toledo et al. 2006). Similar effects were observed in cells exposed to acute low doses of γ rays that were followed by incubation, at 37°C, for periods extending up to 48 h. Accumulating data indicate that DNA repair, oxidative metabolism and cell cycle checkpoints are implicated in the observed biological responses and involve differential regulation of signaling processes. Significantly, proteomic analyses have shown that several proteins are distinctly sensitive to low, but not high, dose γ rays. Furthermore, dissimilar epigenetic events were detected in low- or high dose-irradiated cells and in cells exposed to doses from low or high LET radiations that result in similar survival levels. Notably, studies show that reactive oxygen species (ROS) produced by low dose γ radiation exert similar biological effects as those generated by normal oxidative metabolism (Venkatachalam et al. 2008). The exposure to low dose/low dose rate γ rays restored normal progression in the cell cycle of human fibroblasts wherein signaling pathways that regulate growth under homeostatic conditions were perturbed by the effect of inhibiting NADP(H) oxidase, an important source of ROS in various cell types (Venkatachalam et al. 2008).

With relevance to the assessment of health risks, exposure to low dose/low dose rate ^{60}Co γ rays in the range of 0.1 to 10 coy significantly ($p < 1.9 \times 10^{-5}$) reduced the frequency of neoplastic transformation to below the spontaneous level in C3H 10T½ mouse embryo fibroblasts (Azzam et al. 1996). Interestingly, a dose of 0.1 cGy is in the range of a typical occupational exposure and represents, on average, about one track per cell that is hit, the lowest possible dose that a cell can receive (Bond et al. 1988). Hence, neoplastic transformation data imply that a single low dose exposure, in the background or occupational dose range, can in some circumstances induce processes which reduce rather than increase carcinogenic risk, which is similar to extensive findings by others (Redpath and Antoniono 1998, Redpath et al. 2001).

In experiments designed to examine the propagation of protective effects induced in low dose/low LET irradiated cells, studies in confluent cultures consisting of irradiated and unirradiated normal human cells showed that adaptive effects induced by low dose/low LET radiations, including short-range β particles from incorporated tritium, ^{137}Cs γ-rays or 1GeV protons, were communicated to neighboring non-targeted cells and protected the latter against DNA damages from challenge exposures to γ rays or high charge/high energy (HZE) particles, a high LET radiation.

Using mice, studies have shown that oxidative metabolism and intercellular communication are major mediators of tissue responses to low dose/low dose rate γ rays. Mitochondria, which are active participants in oxidative metabolism, play a crucial role in the induced adaptive responses, which appear to be transient and tissue-dependent. Whereas exposure to acute low doses (10 cGy) transiently decreased some mitochondrial functions (e.g. mitochondrial protein import), exposure to low dose/low dose-rate γ rays enhanced these functions. Accordingly, the observed decreases following acute low dose γ rays may be a protective compensatory response to the initial induced oxidative stress; they occurred in normal cells and not in transformed or cancer cells.

Collectively, the results show that cells can adapt when exposed to low chronic doses of low LET radiation, and the adapted cells are better able to correctly repair DNA lesions resulting from endogenous metabolism or a subsequent challenge exposure and thus less likely to be transformed to the neoplastic phenotype.

In contrast to adaptive responses detected in cells/tissues targeted with low dose/low LET radiations, persistent stressful effects were observed in cells/tissues targeted with high LET radiations, including alpha and HZE particles. Oxidative stress as judged by increased levels of ROS, protein carbonylation and lipid peroxidation, as well as mitochondrial dysfunction

and genomic DNA damage were not only confined to the target but were also propagated to neighboring cells/tissues. Direct intercellular communication through gap junctions (Azzam et al. 1998, Azzam et al. 2001) and indirect communication involving inflammatory cytokines were involved in the propagation of the observed stressful effects, which also persisted in the progeny of bystander cells and led to their transformation to the neoplastic phenotype.

In conclusion, the data support the argument that biological responses together with biophysical considerations predict the outcome of exposure of human and non human biota to ionizing radiation. While similar mediators may modulate the same endpoint in low dose-induced adaptive responses, bystander effects or genomic instability phenomena, the occurrence of opposite effects, such as pro-survival rather than cytotoxic/carcinogenic effects, may reflect changes in concentration of the inducing factor(s), and may also involve distinct mediating factors/mechanisms. The data strongly support a role for radiation dose and radiation quality in determining the nature of the induced effect.

Coupled with epidemiology, knowledge of cellular and molecular processes underlying low dose radiation-induced biological effects should further refine estimates of radiation risks at low doses. These studies are consistent with the concept that mechanistic investigations constitute a significant guide to empirical epidemiological analyses in areas where there is uncertainty.

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