Radiation-Induced Neoplastic Transformation and Cancer Risk Assessment at Low Doses of Low-LET Radiation

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Epidemiologic studies of cancer incidence are insensitive at low doses (<10 cGy). For this reason it is necessary to turn to relevant experimental systems in order to shed light on what may be happening regarding cancer risk at these low doses. In terms of in vitro studies, a cancer-relevant endpoint is neoplastic transformation. Over the past 10 years we have investigated the effects of a range of doses for a variety of sources of low-LET radiation with the goal of determining the shape of the dose-response curve, and underlying biologic responses, at low doses. The first conclusion we have arrived at is the dose-response for high dose-rate radiation is not linear but J-shaped. The transformation frequency only begins to rise above background at doses above 10 to 20 cGy. Secondly, we have evidence that the low dose suppression is most likely a consequence of multiple mechanisms (up-regulation of DNA repair and antioxidant status as well as hyper-radio-sensitivity of cells destined to become neoplastically transformed). Thirdly, we have evidence that this suppression of transformation also occurs for radiation delivered at low (mGy/min) to very low (mGy/day) dose-rates. In addition, we have shown that exposure to very low dose-rate radiation (mGy/day) over 2 to 3 months confers a resistance to neoplastic transformation by a subsequent challenge dose, i.e. an adaptive response as classically defined. It would therefore appear that low doses of low-LET radiation mount responses that protect cell populations against neoplastic transformation in vitro. Clearly, in vitro systems have limitations compared the in vivo situation, nonetheless, they have historically given comparable conclusions at high radiation doses to those seen in vivo in terms of the effect of dose-fractionation, dose-rate, LET and chemical modifiers. A priori, there is therefore no reason to doubt that the same will be true at low doses. Indeed, there are several in vivo studies that would support this contention. Additionally, the relative risk for neoplastic transformation determined from our studies agrees well with those for cancer incidence from radiation epidemiology in the case of breast cancer and leukemia. Based on the above, and other extensive evidence in the literature, it is unlikely that cancer risk from low-LET radiation has a linear-no-threshold dose-response and that threshold, or even hormetic, responses are more probable. Acknowledgement. Supported by the U.S. Department of Energy Low Dose Radiation Research Program.