Chronic Low Dose Radiation Effects on Radiation Sensitivity and Chromosome Instability Induction in TK6 Cells

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There are a number of cell responses that can be detected after low dose radiation exposures including the adaptive response, low dose hypersensitivity, and induced genomic instability. The relationship between these different phenomena is unknown. In this study, we measured adaptive responses, low dose hypersensitivity, and induced genomic instability in a human B-lymphoblastoid cell model, TK6, where we could genetically modify radiation responses by either over-expression of BCL-2 or deletion of TP53. TK6 is a radiosensitive cell line as measured by clonogenic assay. It is also sensitive to apoptosis induction. Deletion of TP53 was associated with a more radioresistant survival phenotype and reduced levels of apoptosis measured 48-h after a 5 Gy gamma ray exposure. Over-expression of BCL-2 in TK6 cells had no effect on cell killing following radiation exposure, but did lead to lower levels of apoptosis 48-h after a 5 Gy exposure.

Cells were exposed to either a single dose of 10 cGy gamma rays or to daily doses of 10 cGy gamma rays delivered over a 3 week period. Chronic low dose exposures were more effective than single exposures in inducing both the adaptive response and genomic instability. Chronic low dose exposure induced a significant increase in radioresistance (adaptive response) in both TK6 cells and in TK6 cells over-expressing BCL-2. It had no significant effect on sensitivity in the TP53 knockout of TK6. Resistance was associated with an increased capacity for repair of sublethal damage and the response decayed back to normal levels ~1 week after the chronic exposures ended. Low dose hypersensitivity was prominent in TK6 cells but much reduced in the other two cell lines. Induction of an adaptive response in TK6 cells reduced the magnitude of the hyper-sensitivity response. The presence of dicentric chromosomes resulting from telomere fusions was used as the marker for chromosome instability. There was an inverse relationship between radiation-induced apoptosis levels and baseline chromosome instability; however, chronic low dose exposure increased instability levels by a similar magnitude in all three cell lines.

These results point to the likely complexity and potential independence in the etiology of low dose radiation responses. The presence or absence of one low dose response cannot easily predict another low dose response. These conclusions are based on the analysis of a single well-defined cell model. Relationships between low dose-induced phenomena in other cell models, tissues, or individuals may be very different.

Table 1. Comparison of Phenotypes

Cell Line	Radiation Sensitivity[1]	Apoptosis Sensitivity[2]	Adaptive Response	Hyper-sensitivity	Baseline Instability[3]	Instability Post-Irradiation[3]
TK6	Sensitive	57.4%	+	+	0.004 ± 0.002	0.027 ± 0.005
BCL-2	Sensitive	33.7%	+	±	0.010 ± 0.001	0.031 ± 0.007
$TP53^{-/-}$	Resistant	7.3%	-	±	0.024 ± 0.005	0.052 ± 0.006

[1]Based on survival curve measurements
[2]Measurement 48 h after a 5 Gy gamma ray exposure
[3]Fraction of cells with unstable chromosome aberrations (mean ± s.e.m.)

The research described herein was supported by the Low Dose Radiation Research Program, Biological and Environmental Research (BER), U.S. Department of Energy, grants DE-FG03-003462908 and DE-FG03-02ER63365.