

Mechanisms underlying cellular responses to low dose/low LET ionizing radiation in primary haemopoietic cells.

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Exposure of biological systems to ionizing radiation can result in myriad of cellular effects including cell death. Potentially far more damaging than cell death to the organism are delayed effects observed in the progeny of cells surviving radiation exposure, which deleteriously affect the stability of the genome. Genomic Instability (GI) is a complex phenotype observed during the development and progression of cancer, and is induced effectively by ionizing radiation. Radiation-induced genomic instability (RIGI) is observed in the descendants of irradiated cells, as a delayed and stochastic appearance of *de novo* chromosomal aberrations, gene mutations and reproductive cell death. GI may additionally be induced in cells not directly irradiated but in communication with irradiated cells. Factors such as cell type, radiation quality, dose and dose rate, all strongly influence the expression of the instability phenotype. Furthermore, there are important genetic components in mouse and man that determine the relative sensitivity of their cells to radiation-induced genomic instability and ultimately their cancer risk. Our current understanding of the link between these genetic mechanisms and GI helps explain the uncertainty in the ability to assess the risk of exposure to low dose/low dose rate ionizing radiations which is due largely to genetic heterogeneity amongst individuals. Numerous studies utilising human cell lines, human primary cells, accidentally-exposed human populations and mouse models, have been performed predominantly using high LET irradiation or high doses of low LET irradiation. However, the interplay between genetics, radiation response and genomic instability has not been extensively examined at very low doses of low LET irradiation.

In this study we have used two strains of mouse which have been shown to differ in their sensitivity to ionizing radiation. This has allowed us to gain an understanding of the role of genetic predisposition to genomic instability following low-dose, low-LET radiation exposure, and make comparisons with high-dose low-LET radiation exposure.

Lysed bone marrow haemopoietic cells from these strains were exposed to X-ray doses from 0.01 to 3 Gy and numerous endpoints associated with the response to irradiation were measured, including apoptosis analysis by annexin v detection; western blot analysis for expression of apoptosis-related and other proteins; chromosomal analysis of metaphase preparations; analysis of colony forming units (CFU-A); cytokine analysis; and gene array analysis.

Results from the extended study showed wide scale differences between the two mouse strains in support of previous study findings, with a clear inverse relationship identified between chromosomal instability and apoptosis in one strain at delayed time post-irradiation. Collectively, findings from protein expression, chromosomal and apoptotic analysis suggest a model for strain specific radiation response; normal DNA damage recognition and repair leading to cell death and reduction of chromosomal instability. Conversely, with normal recognition of damage and abnormal repair leading to increased survival and increased chromosomal aberrations.

Preliminary analysis from pilot studies for cytokine analysis and gene array suggested distinct strain differences, with the latter indicating the role of genes controlling homologous

recombination and metabolic pathways. However, this work requires further confirmation and consolidation with current data.

Overall, the data from these studies suggest influential differences between the immune/metabolomic/ repair status of haemopoietic stem cells post-irradiation in the two mouse strains, and that there are two main types of response to irradiation: 1. responses associated with survival of damaged cells and 2. response associated with elimination of these cells. It is possible that these phenotypic differences are influenced by the genotype of stem cells and/or the haemopoietic microenvironment (i.e. stromal cells).

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