GENETIC CONTROL OF THE TRIGGER FOR THE G2/M CHECKPOINT

Erik Young, Lubomir Smilenov and Eric Hall

Columbia University, New York, N.Y. 10032

At high radiation doses (0.5Gy- 2Gy) there is good evidence that radiation can induce many types of cancer; the best evidence coming from the study of the A-bomb survivors. Present controversy surrounds cancer risks at lower doses below 100 mGy where definitive results from epidemiological studies are not found. An important factor here is the potential contribution of two putative radiation response programs, one operating at higher doses and a second at lower doses.

When normal cells are exposed to a dose of radiation large enough to cause chromosome aberrations, they become arrested at the G2/M checkpoint, and this delay allows repair of damage before the complex task of mitosis is attempted. However, we have previously shown that a considerable amount of DNA damage (and therefore a large dose of radiation) is needed before the G2/M checkpoint is triggered and that after low doses of radiation cells can progress into mitosis without delay. Differential activation of this checkpoint at low versus high doses supports the idea of a separate low dose radiation response program.

It has been known for many years that cells homozygous for mutations in ATM possess neither a competent G2/M checkpoint, nor proficient repair of DNA damage. Employing proliferating mouse embryo fibroblasts with ablated checkpoint control as a model system, we chose to investigate the contribution of various other radiosensitizing alleles to the function of the G2/M checkpoint.

We examined G2/M arrest kinetics in this partially functional system in doses ranging from 10 mGy to 5.0 Gy over a time course of 0 to 12 hours. The array of radiosensitizing genes under investigation now includes Rad9, PTEN and ATM. To date, our findings reveal firstly, that only a dose generating a substantial amount of damage is sufficient to induce G2/M arrest in our system. Secondly, MEFs doubly haploinsufficient for PTEN and ATM activate the G2M/checkpoint with comparable proficiency to those derived from wild type littermates. Our findings also confirm that MEFs nullizygous for ATM have a severely ablated radiation-induced G2/M arrest response.

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