

A MOUSE MODEL APPROACH FOR INTESTINAL TUMORIGENESIS ESTIMATES

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INTRODUCTION

Ionizing radiation is a known risk factor for colorectal (CR) cancer based on studies such as the A-bomb survivor cohort [1]. Considering the high spontaneous incidence of GI cancer in the US and even higher incidence of pre-malignant lesions such as colonic polyps, an even modest increase by radiation exposure could have a significant effect on health risk estimates for manned space flight. One general approach for risk assessment is to determine the RBE of various parameters for space radiation compared to terrestrial radiation exposures. Since there is sufficient statistical sampling for the latter, risk estimates can then be “extrapolated” to space radiation using a RBE scaling factor, which in this case will be intestinal tumorigenesis. While the application of scaling factors is generally accepted to be the only practical approach to human cancer risk estimation for space radiation, a central testable hypothesis is that qualitative and quantitative differences between space radiation and γ -ray effects are maintained across species, such as from mouse to man. Understanding how to scale such risks in model systems will provide the framework for undertaking the same scaling of cancer risks in humans. To use this approach requires collection of quantitative data for oncogenic and pre-oncogenic endpoints in a relevant mouse model system, as well as sufficient understanding of the comparative molecular mechanisms involved in these carcinogenic pathways.

EXPERIMENTAL STRATEGY/RESULTS

The overall plan is to apply a well-characterized mouse model for intestinal tumorigenesis to develop risks estimates for radiation exposures during manned space flight. This will involve a quantitative and qualitative analysis of tumor frequency in the Apc^{Min} mouse model and comparison of HZE particles or protons to equitoxic doses of γ -radiation. As there are very limited data in the literature, an LD50/30 study for HZE radiation was performed in 6-8 weeks old female C57BL/6J mice to determine the doses equitoxic to 2 and 5 Gy of γ -radiation. Mice were irradiated with 0 to 8 Gy of high-energy iron particle at the National Space Research Laboratory at Brookhaven National Laboratory. An LD50/30 for the γ -ray radiation was also studied with our experimental setting in these mice was determined to be 7.5 Gy. The LD50/30 for HZE particle was determined to be 5.8 with an RBE of 1.29.

As prolonged and sustained production of reactive oxygen species (ROS) leading to oxidative stress in the cell has been linked to carcinogenesis [2], these mice were followed for up to 5 months for evidence of chronic oxidative stress both at the tissue as well as organism level. Relevant to intestinal tumorigenesis, the question was if at the intestinal cells of these mice there are differences in γ -ray and HZE induced chronic oxidative stress. Such differences could play an important role in determining the late effects of radiation including tumorigenesis [2, 3]. The mice were observed with regular weight, phenotypic observation, antioxidant status of specific organs and reactive oxygen species in intestinal cells. Western blot analysis for p53, γ H2AX, and SOD was performed to assess the stress response status of the intestinal cells. Genomic instability was assessed by *inter-alu* PCR analysis. For an indication of pathway activation expression profiling was performed by microarray analysis of RNA from γ -ray and HZE irradiated intestinal samples. Our result to date indicates some difference in redox status of γ -ray and HZE irradiated mice and HZE irradiated mice appear to show sustained pro-oxidant environment at the tissue as well as organism level. Radiation tumorigenesis studies are underway in Apc^{Min} mice.

REFERENCES

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