RADIATION ENHANCES AZOXYMETHANE-INDUCED COLON CANCER DEVELOPMENT

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INTRODUCTION

The combined effects of radiation and chemical carcinogen exposure on colon cancer development have not been extensively studied. This is especially true for high doses of radiation or sources of high-energy, heavy ion radiation (high LET), such as that encountered in space beyond low Earth orbit.

MATERIALS AND METHODS

To determine whether prior radiation exposure influences the development of colon cancer caused by a chemical carcinogen, we conducted an experiment using Sprague-Dawley rats in a 2x3 experimental design. Half of the rats were treated with 1 Gy of 1 GeV/nucleon Fe ions at Brookhaven National Laboratory. All the rats were injected with azoxymethane (AOM; 15 mg/kg body weight), a colon-specific carcinogen (alkylating agent) at 10 and 17 d after radiation exposure. Rats were terminated at 4, 6, or 8 wk after the final AOM injection and the colons were resected. Half of the colon was used to determine the number and multiplicity of aberrant crypt foci (ACF), which are considered preneoplastic lesions in colon cancer. The other half of the colon was prepared for mRNA analysis by microarray and PCR analyses. Two, 1-cm sections were removed from the distal colon and fixed for immunohistochemical analysis of proliferation and apoptosis.

RESULTS

The number of high-multiplicity ACF was 57% larger ($P = 0.013$) than the number observed in rats treated only with azoxymethane. The formation of high-multiplicity ACF peaked ($P = 0.0001$) by 6 wk and was maintained through 8 wk. The proportion of proliferating cells was nearly doubled ($P = 0.025$) by radiation at 4 wk, compared with the level found in rats not exposed to radiation. Proliferation was not different between the irradiated and non-irradiated rats by 6 and 8 wk. Although radiation, when combined with AOM, enhanced the rate of proliferation earlier than AOM alone, there was no interaction between radiation treatment and time after AOM exposure on ACF formation. Radiation altered the expression of a variety of genes involved in detoxification, inflammation, and cell cycle regulation. The interaction of time and radiation treatment was significant for 42 transcripts of known function.

DISCUSSION

These data indicate that galactic cosmic radiation enhances colonocyte sensitivity to subsequent alkylating agent exposure, making the risk of colon cancer development greater in individuals exposed to 1 Gy of 1 GeV/nucleon iron ions. Thus, astronauts will need to be protected from exposure to this level and type of radiation if their health is not going to be compromised. Since shielding personnel from exposures may not be a possibility, then countermeasures will need to be implemented to reduce the damage and slow progression of any neoplasias caused by the radiation. Surveillance will have to be implemented to detect early neoplasias of returning long duration astronauts. This study also highlights the importance of examining the interactions of different carcinogens and supports the need for better characterization of mixed environmental hazards to humans for risk estimation.

ADDITIONAL INFORMATION

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