UPDATE OF HARDERIAN GLAND TUMORIGENESIS: LOW-DOSE- AND LET-RESPONSE

P. Y. Chang[1,2], K. A. Bjornstad[2], J. Bakke[1]. C. Rosen[1], N. Du[2], D. Fairchild[2], and E. A. Blakely[2]
[1]Biosciences Division, SRI, International, Menlo Park, CA 94025,
[2]Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720

INTRODUCTION AND APPROACH

Increased cancer risk remains a primary concern for travel into deep space and may preclude manned missions to Mars due to large uncertainties that currently exist in estimating cancer risk from the spectrum of radiations found in space with available human epidemiological radiation-induced cancer data. The goal of our project is to reduce uncertainties in the Relative Biological Effect (RBE) and Linear Energy Transfer (LET) relationship for particle radiation carcinogenesis. The historical Harderian Gland (HG) tumor prevalence data in female CB6F1 (C57Bl/6J x BALB/CJ) mice from studies of Fry et al. [1], and Alpen et al. [2] represent the most complete set of experimental observations and dose dependence available on a specific radiation-induced tumor in an experimental animal using beams of heavy ions that are found in the cosmic radiation spectrum. However these data are lacking complete information on low dose responses below 50 cGy and in the LET region between 25 and ~190 keV/μm. Our approach is to use these existing data on HG tumorigenesis as a reference, and fill in the gaps in knowledge in the low dose and missing LET range to improve our understanding of the dose-response curve at low doses and test our results for deviations from linearity.

METHODS

Female CB6F1 hybrid mice were purpose-bred and irradiated or sham-treated at ~100 days old with low (≤ 32 cGy) doses of 260 MeV/u Silicon ions (LET ~70 keV/μm), or with low (≤ 26 cGy) doses of 1 GeV/u Titanium ions (LET ~100 keV/μm) at Brookhaven National Laboratory's NASA Space Radiation Laboratory. Animals were monitored daily and weighed weekly until necropsy 16-months post treatment. Complete necropsies were completed and major organs, including tumor tissues and those with gross observations were harvested and either snap-frozen, or fixed for additional study. HG, lung and tissues with gross observations were blocked and slides were prepared for comprehensive evaluation by a board-certified veterinarian histopathologist. The HG tumor tissues were exhaustively sliced 5 μm thick and slices were taken every 75 μm throughout the tissue to reveal all tumors present in each tumor.

RESULTS

Our results show that (1) the spontaneous HG tumor frequency in our study is consistent with the prior published frequency; (2) the increase in HG tumor incidence as a function of low Si- and Ti-doses show dose-dependent structure that are consistent with the trend established by Alpen et al. [2] with the dose responses of the Ti-ions and Si-ions each nesting below the results published incidences for 193 keV/μm (600 MeV/u Iron ions), and above 25 keV/μm (670 MeV/u Neon ions); (3) Histology of the HG tumors after both Si and Ti-ion exposure revealed primarily benign papillary adenomas, with a small percentage of carcinomas in the sham-treated controls and higher dose groups; and (4) Si-induced lung tumor incidence revealed non-linear dose dependence, while preliminary Ti-ion results suggest that there are no statistically significant increases in lung tumor incidence with increasing dose compared to the unirradiated controls; (5) Histological evaluations of both Si- and Ti-ion induced lung tumors revealed benign bronchio-alveolar adenomas were prevalent, with small percentages of bronchio-alveolar adenocarcinoma, histiocytic/reticulum cell carcinoma and lymphoma in the higher doses.

CONCLUSIONS AND FUTURE DIRECTIONS

Our study has contributed to filling in gaps of HG tumor incidence at low fluences of high-energy particle beams at 70 and 100 keV/ μm. We have obtained additional information regarding ion-dependent lung, tumor incidence in other organs, and particle-dependent differences in tumor histologies. Additional animals exposed to fractionated Ti-ions, Iron ions and ^{137}Cs gamma rays will be processed in 2014. Results from these studies will allow a final comprehensive analysis and theoretical modeling of the data for best fits.

REFERENCES

[1] Fry, R.J.M., et al. (1983) *Adv Space Res* 3, 241-248. [2] Alpen, E.A. et al. (1993) *Radiat Res* 136, 382-391.

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