Non-Targeted Effects and the Dose Response for Heavy Ion Tumorgenesis

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Abstract

BACKGROUND

There is no human epidemiology data available to estimate the heavy ion cancer risks experienced by astronauts in space. Studies of tumor induction in mice are a necessary step to estimate risks to astronauts. Previous experimental data can be better utilized to model dose response for heavy ion tumorgenesis and plan future low dose studies.

OBJECTIVES

- To describe new experimental data that improve understanding of tumor induction in mortal mice
- To develop models that use combining data for all ions to strengthen the individual ion models
- To estimate the radiation quality at a variety of low doses to improve understanding of tumor induction

METHODS

- Measured Harderian gland tumors in female B6CF1/Anl mice
- A variety of heavy ions were accelerated at the Lawrence Berkeley National Lab for the exposures.
- Mice were irradiated at 100 to 120 days.
- Tumor prevalence was determined by stimulating tumor response
- Tumor appearance was accelerated by using pituitary implants

RESULTS

1. Three radiation doses (D1, D2, and D3 from figure) were considered and d = 2%
2. Three radiation doses were considered and d = 1%
3. Four radiation doses (D1, D2, D3, and D4 from figure) were considered and d = 2%

Power Analysis

- The study focuses on low dose where the cell sterilization term can be ignored.
- Simulations were analyzed using linearized models with bystander terms to detect NTE
- Power was determined by the ability to detect if NTE effects (x) are significant at low dose
- Doses were chosen at 0Gy and 3 or 4 irradiation doses as seen in the figure with sample sizes such that all doses have equal binomial variances
- Sensing Doses for irradiated mice:
  1. Three radiation doses (D1, D2, and D3 from figure) were considered and d = 2%.
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Table: Sensitivity of sample size to detect NTE with 80% power to the scheme choice and background in prevalence (P).

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<th>Scheme</th>
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Heavy Ion NTE model relating dose and LET to tumor prevalence

- The optimal design to detect a NTE for an individual ion had 4 doses equally spaced below a maximal dose where "bending" due to cell sterilization was < 2%.
- For example at 100 keV/micron we would irradiate at 0.03 Gy, 0.05 Gy, 0.13 Gy, and 0.26 Gy and require 850 mice including a control dose for a sensitivity to detect NTE with 80% power.
- Sample sizes could be improved by combining ions similar to the methods used with the Harderian gland data.

Color Categories

Uncertainty Reduction/Risk Mitigation Category Color =
- Description of Ion Data

Heavy Ion NTE model relating dose and LET to tumor prevalence

- The usage of human cell culture models in 2D or 3D is needed to support the applicability of murine models to human risk prediction.
- Power analysis based on the Harderian gland data of Alpen et al. [1-3] was reanalyzed [4] using non-linear least square regression. The data set measured the induction of Harderian gland tumors in mice by high-energy protons, helium, neon, niobium, and lanthanum with LET’s ranging from 0.4 to 950 keV/micron.
- We were able to strengthen the individual ion models by combining data for all ions in a model that relates both radiation dose and LET for the ion to tumor prevalence.
- Compared models based on Targeted Effects (TE) to one motivated by Non-targeted Effects (NTE) that included a bystander term that reduced the effects of competing tumor risks and reduced costs of experiments (sacrifice at 600 compared to lifespan of ~900 days).
- Fe nuclei showed same tumor response with or without the bystander term that can be ignored.
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Blue Bullets Progress

- Applying a NTE model motivated by the dose response observed for bystander effects and genomic instability in cell culture, we show that the NTE model provides a superior fit for the dose response for tumors in mice based on several model ranking tests. These results add important empirical evidence in support of the NTE model based on living data for tumor responses.
- We were able to fit models for the LET dependence of tumors over a broad range from protons to heavy ions and describe a dose response RBE applicable to low dose exposures.
- Power analysis based on the Harderian gland data suggest the optimal number of mice to be studied for future dose response experiments and suggest sample size reductions will occur when several radiations are combined into a single model.

Red Bullets Gaps in Progress and Knowledge

- The relative contribution to cancer risks from targeted effects and non-targeted effects remains elusive with too few experiments designed to test the shape of the dose response at low doses (0.3 Gy) applicable to space missions.
- Only a few murine model tumors have been studied with only a few ion types. The paucity of data limits the building and testing of models of cancer risk from space radiation.
- The usage of human cell culture models in 2D or 3D is needed to support the applicability of murine models to human risk prediction. However, much work remains in making the necessary connections. Of importance is the need for more expansive data set on radiation quality at a variety of low doses to understand the shape of the dose response for cancer processes induced by heavy ions.