STOCHASTIC MODELS OF SPACE RADIATION DNA DAMAGE RESPONSES AND CANCER RISKS

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Abstract:

On space missions astronauts are exposed to a steady flux of galactic cosmic rays (GCR) consisting of high-energy protons and heavy ions. In the next decades long-term missions of up to 200 days to the Earth's moon and 1100 days to Mars are planed by NASA where cumulative doses will not be low (>100 mSv) albeit dose-rates are small (1-3 mSv/d). Mission costs are increased by uncertainties in risk projections due to the need to provide adequate safety margins. Currently uncertainties in space radiation risk estimates are large because of the poor understanding of the biological effects of heavy ions and the imprecision of approaches based on low-LET epidemiology data, and relative biological effectiveness factors (RBE) and dose- and dose-rate effectiveness factors (DDREF). Estimates of cancer risks for space radiation, including ones which update models based on the BEIR VII report, contain uncertainties large enough to preclude a decision on Mars exploration at this time thus providing an important impetus for research aimed at uncertainty reduction.

In order to reduce the uncertainties in space radiation risk estimates and determine the validity of models which scale to low-LET data, NASA needs to know how molecular events related to DNA damage and repair, cell signalling, and tissue response pathways occur after single tracks of heavy ions traverse cells and tissues, and if such events differ significantly enough to preclude any scaling approach using low-LET epidemiology data. We describe methods that incorporate systems biology approaches with stochastic models of particle tracks to improve our understanding of these events. Systems biology models that describe protein regulatory networks using non-linear biochemical kinetics are described for the non-homologous end-joining and homologous recombination pathways and are coupled to systems models of cell cycle progression. Particle track structure models that consider the proportions of simple and clustered DNA damage, and their distribution throughout individual chromosomes, whole cells and tissues are described. To test our stochastic systems biology approach, we consider Monte-Carlo computer simulations that compare to experimental data for the temporal and spatial distribution of radiation induced repair foci measured with confocal microscopy or flow cytometry. Relevant differences between low LET and high LET radiation tracks are discussed.

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