

The use of human epithelial cells and mouse models of human lung cancer for space radiation research

Jerry W. Shay
Professor, UT Southwestern Medical Center
Department of Cell Biology
5323 Harry Hines Blvd.
Dallas, TX 75309

Email: Jerry.Shay@UTSouthwestern.edu
Phone: 214-648-3282

Lung cancer is the most prevalent form of cancer in both males and females and presents one of the largest targets for radiation effects. Estimates based on atomic bomb data suggest that extended single low orbit missions at an average astronaut age of 42 would result in a 100-fold increase lifetime risk of developing lung cancer (even in never smokers). Recent estimates by NASA suggest that the incidence and mortality of lung cancer due to irradiation exposure is the highest of all solid cancer types. NASA needs to know how experimental models of tumor development for all cancers including lung cancer can be developed so that data from terrestrial radiation can be extrapolated into human risk projections for long-term missions in deep space. The mixed fields in space create many uncertainties related to quality and dose-rates of solar particle events and galactic cosmic radiation. In addition there are age and gender dependencies of cancer risk including inter-individual differences. Thus, NASA needs new research in order to model increases in risks of fatal cancers for both acute and late effects of space radiation exposures. The current guidelines indicate that human total radiation exposures must be limited to an overall of no more than a 3% increase in fatal cancer risks. The current permissive exposure limits for fatal cancer risks are currently projected to be violated for a Mars mission under all possible scenarios. Thus, there is an immediate need for new research results to modify the uncertainty reductions in risk projection models and if needed the development of biological countermeasure.

In our laboratory we have been examining both human lung epithelial cells in cell culture (2D and 3D organotypic models), to assess specific steps in lung cancer initiation and progression. These include transformation assays such as anchorage-independent cell growth, cell motility and invasion assays and making human tumors in immunosuppressed mice (xenograft experiments). In addition, we have utilized mouse models that are susceptible to the development of lung cancer and are testing solar particle event simulations and exposure to single acute or fractionated/protracted galactic cosmic irradiation to determine if there are increases in the incidence or progression of lung cancer in vivo. Most scientists agree that there is unique damage to biomolecules, cells and tissues due to space irradiation, but the mechanisms by which radiation damage develops into health risks are poorly understood. While effective shielding can reduce the space radiation problem, it will not eliminate it and thus animal models and better cell-based models must be applied or developed to permit modeling of the estimates of cancer risk as well as many other risks, such as for the CNS, cardiovascular system, bone structure etc. Our work has demonstrated that there is unique gene expression patterns associated with the space radiation particle spectrum such that different beam types produce different expression signatures. We have also determined that high LET radiation (^{28}Si , ^{56}Fe) at 0.25 Gy (1GeV) leads at 4 months to an ~50-100 fold increase in the soft agar transformation rate in the human lung epithelial cell model. Comparing DNA damage in 2D to 3D we have found more persistent DNA damage in 3D cultures from space radiation. We hypothesize that persistent DNA damage will result in genomic instability that will promote the loss of tumor suppressors or activation of oncogenes. The persistent damage could also

lead to selection pressure for the abrogation of DNA repair and checkpoint mechanism. The net outcome will be a high degree of cellular transformation and tumorigenesis in response to space radiation.

Our work on mouse models is important since we can interrogate the microenvironment including inflammatory responses, stem cell niches, background, age and gender difference as well as intra-individual responses. We have observed that fractionated ^{56}Fe exposure (1Gy, 1GeV over 5 days) resulted in a statistically highly significant increase in invasive cancer compared to single acute doses of ^{56}Fe exposure (1Gy, 1GeV). This could be due to a role of stem cell repopulation for lung tissue that is important in cancer progression. Acute dosages of high-LET ions may increase cell killing, reducing the number of target stem-like cells available for cancer progression. Another hypothesis we are testing is that fractionated charge particle irradiation but not single dose irradiation may lead to amplified local chronic inflammatory signaling that may increase the probability of progression to invasive carcinoma.

Immune cells, which often infiltrate tumors and preneoplastic lesions, produce a variety of cytokines and chemokines that propagate a localized inflammatory response and also enhance the growth and survival of premalignant cells. We have conducted a large microarray study comparing single acute versus fractionated irradiation and have developed an inflammatory signature that we are currently testing. Identification of such inflammatory modulators may offer preventive (countermeasure) or therapeutic approaches in the future.

The immediate objective of our current investigations is to obtain new research that will help to reduce the uncertainties for risk of developing space radiation induced lung cancer. It is important to note that risk is not measured; it is predicted by a model. Thus, the new research findings should be very helpful to NASA to model such risks and if they are too high to develop biological countermeasure to permit more safe days for astronauts in space.

JERRY SHAY - NASA SUMMER SCIENTIST