Development of a Risk Assessment Model for Lung Cancer Pathogenesis after Exposure of Human and Mouse Lung Epithelial Cells to HZE Particle Radiation

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Overall Goal: The goals of our NSCOR research program are to discern the molecular and cellular events associated with and participating in the multi-step process of lung cancer pathogenesis, after exposure to the unique radiations associated with long-term manned space exploration. The data generated here, as well as other data from the UTSW NSCOR, are being used to develop a more accurate model of lung cancer risk from HZE radiation exposure.

Approach: We are using molecular and cell biologic approaches in human and mouse models systems to address this problem. These include: 1. Development of a unique panel of immortalized human large and small airway epithelial cells derived from over 50 individuals (human bronchial epithelial cells, HBECs, and human small airway epithelial cells, HSAECs) that have also been genetically manipulated with defined oncogenic changes found in lung cancer to derive isogenic variants representing the preneoplastic steps found in lung cancer; 2. Development of 2D and 3D in vitro systems permitting the study of the effects of HZE particle radiation on HBECs and HSAECs in tissue like structures; 3. Characterization of the response and survival of these cells to various types of γ and HZE particle radiation; 4. Detailed genome wide molecular profiling studies (mRNA, miRNA, DNA copy number, methylation, protein) of these cells before and at different time points after radiation; 5. Cell biologic tests of the progression of these cells toward the malignant phenotype including soft agar colony growth and the development of epithelial to mesenchymal (EMT) transition; 6. In vivo tests of tumorigenicity; 7. Use of novel transgenic mouse models of lung cancer to explore the development of lung cancer in a whole animal model after different types, doses, and schedules of HZE particle and γ radiation; 8. Establishment of an integrated database of the large volume of data accumulated; 9. Statistical and modeling analysis of the data to establish quantitative elements of the risk of progressing towards lung cancer after HZE particle and γ radiation.

Major Questions Being addressed: We have focused on several major questions. 1. Is there an increased risk of progression toward lung cancer in human and mouse tissues with HZE particle radiation and, if so, what are the quantitative risk estimates for this by dose and schedule? 2. What are the molecular correlates of space radiation induced tumor progression and how do these compare with non space radiation induced lung tumorigenesis? 3. How do the findings of lung cancer development in human tissues and in the whole mouse model compare? 4. What does a model look like that integrates all of these findings? 5. What does a model look like that integrates all of these findings?

Major Findings: We have made several major findings: 1. HZE particle radiation does indeed progress both normal lung epithelial cells (in vitro) and mouse lung cells (in vivo) toward lung cancer and this progression is more with HZE particle than with γ radiation; 2. That dose and particle type play a role; 3. Introduction of known oncogenic changes in HBECs gives such pronounced transformation changes that little additional effect of any type of radiation can be detected; 4. That dose schedule plays a role in vivo; 5. That there are defined gene expression changes following HZE particle radiation that are radiation type specific; 6. That HZE particle induced tumorigenesis is associated with EMT; 7. That dose schedule in vivo results suggest an effect of HZE particles on the tumor microenvironment and that the inflammatory mRNA signatures found in mice actually provide prognostic information in human patients with lung cancer; 8. That the specific molecular changes identified provide a clear path to understanding the mechanism of lung tumorigenesis after HZE particle radiation; 9. That the quantitative changes towards malignancy are reproducible enough to allow development of a risk assessment model. All of these findings provide important new information for NASA’s goal of risk assessment for space exploration.