Role of p53 in Lung Carcinogenesis after Exposure to Space Radiation

E. J. Moding[1], L. Z. Woodlief[2], C. L. Lee[1], Y. Ma[2], D. G. Kirsch[1,2]

[1]Department of Pharmacology and Cancer Biology (everett.moding@duke.edu), [2]Department of Radiation Oncology (david.kirsch@duke.edu), Duke NASA Specialized Center of Research, Duke University Medical Center, Durham, NC 27708

Lung cancer is the most common cause of cancer deaths world-wide and a major site of interest for solid cancer risk estimates after exposure to high charge and energy (HZE) radiation in space. The tumor suppressor p53 and proto-oncogene Kras are the most commonly mutated genes in human lung cancer. Although the mechanisms of HZE radiation-induced carcinogenesis are poorly understood, cancer induced by terrestrial radiation is regulated by p53. To investigate the role of p53 in HZE radiation-induced lung cancer, we are genetically manipulating p53 levels in mice predisposed to non-small cell lung cancer. "Super p53" mice with an extra copy of p53 have increased expression of the p53 transcriptional target p21 after exposure to 1 Gy of 600 MeV/nucleon ^{56}Fe. We have crossed these mice to LA-1 Kras^{G12D} mice that undergo spontaneous recombination to express oncogenic Kras and develop primary lung adenomas and thymic lymphomas. We have exposed WT p53; LA-1 Kras^{G12D} and super p53; LA-1 Kras^{G12D} mice to whole body irradiation with five daily 1.2 Gy fractions of 320 kVp X-rays or five daily 0.2 Gy fractions of 600 MeV/nucleon ^{56}Fe and are monitoring them for tumor initiation and progression. In addition, we are using *in vivo* shRNA against p53 to temporarily or permanently knockdown p53 during radiation exposure to investigate when p53-mediated tumor suppression is required to prevent HZE-induced lung cancer development and progression. We will present an update of our ongoing experiments with respect to lymphoma and lung cancer development.