Role of p53 in Lung Carcinogenesis after Exposure to Space Radiation

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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 ⁵⁶Fe. We have crossed these mice to LA-1 Kras⁶¹G¹²D mice that undergo spontaneous recombination to express oncogenic Kras and develop primary lung adenomas and thymic lymphomas. We have exposed WT p53; LA-1 Kras⁶¹G¹²D and super p53; LA-1 Kras⁶¹G¹²D 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 ⁵⁶Fe 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.