Biological Countermeasures of Space Radiation-induced Invasive Carcinomas in Mouse Models of Lung and Colon Cancer

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Using lung and colon cancer susceptible mouse models we examined the effects of space radiation on cancer progression. The murine LA-1 model expresses mutated *KRAS* in a subset of lung cells resulting in initiation and formation of lesions that mimic lung cancer progression in humans. About 9% of LA-1 129sv mice spontaneously develop invasive non-small cell lung adenocarcinomas. We have compared this lung cancer mouse model with another mouse model of susceptibility to colorectal cancer. About 6% of CDX2P-NLS Cre; $APC^{+/loxP}$ (CPC;Apc) BL6 mice spontaneously develop invasive cancers. Very limited data are available on progression of cancer susceptible mice to more advanced, perhaps fatal, invasive cancers after space irradiation (IR).

Studies included whole body proton IR as a single 2.0 Gy dose (50 MeV and 150 MeV) and as a simulated solar particle event (SPE), of 2.0 Gy over 2 hours with a wide range of energies (50 MeV-150 MeV). Histopathological analysis of the LA-1 and CPC;Apc mice one year post-IR demonstrated a progression in tumor grade to invasive adenocarcinomas (lung from 9-30% and in the colon from 15-26%).

CDDO-EA is an oral available anti-inflammatory/anti-oxidant modulator that has been tested in humans in a variety of clinical trials. We tested if the LA-1 and CPC;Apc mice fed CDDO-EA diet prior to proton or ^{56}Fe- IR would have a lower incidence of invasive carcinoma. In the LA-1 mice fed CDDO-EA prior to 2.0 Gy SPE simulation, the incidence of invasive cancers was reduced from 30% to 19%. In the LA-1 mice feed CDDO-EA prior to^{56}Fe- IR (provided by 5 days of 0.2 Gy per day) the incidence of invasive cancer was reduced from 35% to 17%. To test the generality of the CDDO-EA protection observed in the LA-1 lung cancer progression model, we then tested the CPC;APC mice that have a background incidence of 6% invasive cancer. When the CPC;Apc mice were fed CDDO-EA prior to 2.0 Gy SPE simulation, the incidence of invasive cancers was reduced from 26% to 9.7%. These mice were only fed CDDO-EA prior to IR and one day post-IR. These results indicate that exposure to solar particle IR and ^{56}Fe- IR increases the risk of invasive cancers in cancer susceptible mouse models, and that radioprotectors such as CDDO-EA may reduce the overall risk of fatal cancers.

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