Space Radiation Induced Neuroinflammation on Alzheimer and Parkinson Disease Pathology

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Activation of the innate immune system in the central nervous system (CNS), a process known as neuroinflammation, is a fundamental response to brain injury. Accumulating evidence suggests that neuroinflammation is a critical component of many CNS diseases, including Alzheimer's and Parkinson's, the two most common age-associated neurodegenerative conditions. In particular, there is clear consensus that activation of microglial cells and associated proinflammatory cytokine expression and oxidative injury occurs in these diseases, and work in rodent models as well as epidemiological evidence in people suggests that anti-inflammatory and anti-oxidant therapies may be of benefit. Moreover, recent data from several laboratories, including our own, reveals that local CNS as well as systemic inflammation can dramatically influence Alzheimer's and Parkinson's associated pathology.

Given evidence that neuroinflammation contributes to neurodegenerative pathology and space radiation can elicit neuroinflammatory changes, an obvious question is whether space radiation might exacerbate age-associated neurodegenerative diseases such as Alzheimer's and Parkinson's. Indeed, we found that APP/PS-1 double transgenic mice showed increased amyloid beta plaque pathology and poorer performance on cognitive tasks after exposure to 100 cGy ^{56}Fe at 1 GeV/u (Cherry *et al*., PLoS One 7:e53275, 2012). Based on these finding, we propose to explore the following two hypotheses: **Hypothesis 1:** Space radiation, at doses anticipated with long missions, will exacerbate pathology and behavioral changes in age-associated neurodegenerative diseases such as Alzheimer's and Parkinson's; and **Hypothesis 2:** Space radiation induced inflammatory responses and persistent oxidative stress enhance CNS degenerative changes and lead to impaired performance in susceptible individuals.

Specific Aim 1. We will determine whether space radiation alters CNS pathology and behavioral endpoints in an established transgenic murine model of Alzheimer's disease that harbors three human mutant genes: APPswe, PS1dE9, and tau P301L. These "triple transgenic mice" exhibit both plaque and tangle pathology, representing the two principal neuropathological hallmarks seen in Alzheimer's disease. Groups consisting of twenty triple transgenic mice (10 male, 10 female) at 26 weeks of age were exposed to whole body irradiation with two HZE radiation beams (Iron, 600 MeV/u or Silicon, 300 MeV/u) utilized at each of two doses (10 or 100 cGy) or one proton beam (SPE Event, 200 cGy total dose) during NSRL13C. Two sets of 20 non-irradiated mice were included in the experiment. Mice will be sacrificed at 18 months of age. Histological endpoints will include quantitative measures of amyloid plaque deposition, tangle pathology, and glial activation. Behavioral endpoints will be contextual fear-conditioning and object recognition.

Specific Aim 2. We will determine whether space radiation exacerbates pathological and neurobehavioral measures of nigrostriatal degeneration in a recently developed murine model of Parkinson's disease harboring truncated human parkin (Parkin-Q311X). Radiation and doses will be similar to those listed above, and will be administered to 26 week old transgenic and wild type mice in NSRL Run 14A. The experimental plan will include 20 mice per group (10 male and 10 female). Behavioral testing (locomotor activity) and sacrifice will occur 12 months later. Histological endpoints will include quantification of dopaminergic neurons in the substantia nigra and density of dopaminergic processes in the striatum as well as glial activation.

Specific Aim 3. Frozen tissues secured from appropriate brain regions of mice irradiated in Aims 1 and 2 will be processed for quantitative RT-PCR using a custom 24-gene array to measure a panel of established markers for neuroinflammation and oxidative stress. Changes in gene expression will be correlated with alterations in respective neuropathologies and behavioral endpoints as quantified in Aims 1 and 2.

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