

Fractionated ionizing radiation skews differentiation of glial / oligodendrocyte progenitor cells and induces cognitive defects

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NASA's radiation research program emphasizes understanding of the mechanisms of radiation-induced DNA damage. As radiation research on the central nervous system (CNS) has predominantly focused on neurons, with few studies addressing the role of glial cells, we have focused our research on identifying the major DNA repair pathways induced by oxidative stress due to high atomic number (Z) and energy (HZE) radiation in glial cells. Ionizing radiation (IR) causes degeneration of myelin, the insulating sheaths of neuronal axons, leading to neurological impairment. Recent data with lower doses of ⁵⁶Fe particle radiation not only show dose-dependent decrease in viable neurons (like X-rays), but also reveal an adverse effect on astrocytes and OL progenitor cells (OPC). However, with higher doses, there was an increase in the proportion of OPC-derived astrocytes, suggesting astrocytosis. Thus, astronauts exposed to protons and HZE radiation risk adverse effects during their missions as well as latent health effects. Moreover, patients undergoing fractionated radiotherapy show higher DNA repair activity in their normal cells, in contrast to their tumor cells. Both of these irradiated human cohorts would benefit from an increased understanding of DNA repair. Because base excision DNA repair (BER) is a pathway up-regulated in response to oxidative stress by low-LET radiation, it is essential to determine how high-LET-induced BER affects the fate of OPC. BER is even more important in mitochondria, the predominant sites of oxidative metabolism, where other DNA repair pathways are more limiting or absent. Since our studies show significant induction of the central BER enzyme apurinic endonuclease-1 (APE1) with dose fractionation, we plan to develop APE1 as a radiation biomarker to quantify these changes and predict radiation risks to CNS. Also, we find that X-rays, protons and HZE exposure inhibits glial progenitor cell differentiation *in vitro*, which may be due to higher APE1 induction along with lowering of mitochondrial membrane potential. Our similar *in vivo* studies with rat spinal cords exposed to single doses of X-rays/HZE indicate demyelination at 1.5 months and these animals also showed significant defects in cognition as measured by Novel Object Recognition Testing (NORT) 9 months post exposure. At present, studies are underway to determine if the spinal cord microscopic observation can be further confirmed by *in situ* cell markers of OPC differentiation, and also be corroborated with inhibition in differentiation *in vitro* of OPC isolated from rat spinal cords, possibly resulting in astrocytosis, higher immature OL and lower mature OL formation, leading to demyelination over time.

Acknowledgements: This work was supported by NASA grant (NNA10DA32I to M. Naidu). We would like to thank all the NSRL support teams at Biology, Collider Accelerator and Medical departments. We thank Dr. Louis Pena of Medical department for his suggestions and data on previous studies done on CG-4 and rat spinal cord. Finally, many thanks are due to Ellie Blakely, Lora Green (posthumous), Betsy Sutherland (posthumous), Edouard Azzam, Charles Limoli, John Fike and Gregory Nelson for their excellent suggestions and piggyback beam time (Sutherland and Green).