FRACTIONATED PROTONS AND HZE RADIATION TO RAT SPINAL CORDS INCREASES BASE EXICISION REPAIR, INDUCES DEMYELINATION, NEUROINFLAMMATION IN BRAIN, COGNITIVE DEFICTS AND NON-TARGETED TUMOR INDUCTION

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NASA's radiation program emphasizes understanding 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 ^{56}Fe 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 repair in 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 inhibit glial progenitor cell differentiation *in vitro*, which may be due to higher APE1 induction along with lowering of mitochondrial membrane potential. APE1 inhibited (at 30%) glial progenitor cells, which had lower mitochondrial membrane potential (than control cells) also senesced within 2-4 days after exposure of both single/ fractionated dose of X-rays/ HZE / protons. Our similar *in vivo* studies with 10-12 month rat spinal cords exposed to single/ fractionated doses of X-rays/ HZE/ protons indicate demyelination at 1.5- 3 months and these animals also showed significant defects in cognition as measured by Novel Object Recognition Testing (NORT) 1.5- 9 months post exposure, increased defect with fractionation for both ^{28}Si and Protons but not for ^{56}Fe. Brains of the X-rays and Protons exposed rats (only at spinal cords) reveal significant increase in neuro-inflammation in all regions of the brain. Also several of 300 MeV/n Si exposed rats developed tumors of brain/ gonads. There was also a differential effect observed with short term potentiation in rat brain slices from proton versus ^{56}Fe exposed rats. Lastly, the spinal cord sections show increase in signal and nuclear localization APE1 with fractionation, with decrease in progenitor cells with an increase in immature OL staining in these sections. Inflammation also resulted in skewing of progenitor cell differentiation, which was confirmed by in situ cell markers, leading to demyelination over time.

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