Persistent Changes in Neuronal Structure and Synaptic Plasticity Caused by Proton Irradiation

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Exposure of the CNS to ionizing radiation typically occurs in the clinical setting, and is used routinely to control the growth of primary and secondary brain tumors. Unintended side effects of radiation exposure to the CNS have been linked to progressive and debilitating impairments of cognitive function that resemble neurodegenerative conditions associated with changes in synaptic plasticity. In part due to the beneficial dose-depth distributions that may spare normal tissue sequelae, the use of protons to treat CNS and a variety of other tumors is rapidly gaining popularity. Protons also pose potential CNS risks to astronauts exposed to these energetic particles during travel within and outside the protective magnetosphere. To explore the potential impact of proton irradiation on hippocampal neurons, and to gain mechanistic insight into the basis of radiation-induced cognitive dysfunction, studies were undertaken to assess the impact of whole body irradiation (0.1 and 1 Gy) on a range of micromorphometric parameters in mice 10 and 30 days following exposure. At these relatively low doses, dose-dependent reductions in dendritic complexity were found, where by day 30, significant reductions (~33%) were found for all morphometric parameters measured (dendritic length, branches, area). At these same doses and times significant reductions in the number (~30%) and density (50-75%) of dendritic spines on hippocampal neurons of the dentate gyrus were found. While immature filopodia exhibited the greatest sensitivity (2-3 fold) to irradiation compared to more mature spine morphologies at each time analyzed, significant reductions in more mature spines (long) were also found 30 days after exposure to 1 Gy. Irradiated granule cell neurons spanning the subfields of the dentate gyrus showed significant and dose-responsive reductions in synaptophysin expression at presynaptic sites in the dentate hilus, while significant and dose-dependent increases in post-synaptic density protein (PSD-95) were found along dendrites in the granule cell and molecular layers. These findings corroborate much of our past work using photon irradiation, and demonstrate for the first time, dose-responsive changes in dendritic complexity, spine density and morphology and synaptic protein levels following exposure to low dose whole body proton irradiation. As many of these changes resemble the types of changes found in a range of neurodegenerative disorders, we assert that radiation-induced changes to the dendritic tree that alter spines and synaptic proteins alter the morphologic determinants of learning and memory to hasten the onset of neurocognitive sequelae.

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