Consequences of low dose irradiation in the CNS

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Radiation-induced oxidative stress can impact the physiologic function of multipotent neural stem and precursor cells by activating redox-sensitive signaling cascades that can alter radiosensitivity, mitochondrial function, and cell fate. Many of these signaling pathways depend on the nature, magnitude and duration of the specific reactive species involved, features that dictate in large part whether radiation-induced changes are harmful or beneficial to the organism. We have shown that acute low dose irradiation (2-20 cGy) can elicit significant increases in reactive oxygen (ROS) and nitrogen (RNS) species over several days to weeks. These redox changes can alter antioxidant (MnSOD) levels, proliferation, survival and differentiation, and can be attenuated further by protracting the dose using a ^{57}Co flood source, by a variety of multidosing paradigms, or by using genetic models deficient for key antioxidant enzymes (EC-SOD). Flood source exposure (5-20 cGy) of human neural stem cells promotes cell proliferation (and possibly survival) by 5-20%. Similar enhancements to survival are found when cells are primed with low dose irradiation, (2-10 cGy) and allowed to adapt from 6 to 48h before exposure to another higher challenge dose (1-5 Gy). Enhanced survival is temporally coincident with radiation-induced oxidative stress (~1.3-5 fold over baseline), increased MnSOD, and more efficient removal of DNA DSB repair foci (γ-H2AX). Moreover, beneficial adaptive changes are enhanced in the EC-SOD deficient background, findings that emphasize the importance of redox state in regulating the radioresponse of neural stem cells. Metabolic changes caused by low dose irradiation can also be quantified by 2-photon spectroscopy as the cellular metabolic index (CMI), defined as the ratio of oxidized flavoprotein (Fp) to reduced nicotinamide adenine dinucleotide (NAD(P)H). Low dose irradiation caused a marked drop in the CMI 1-2 days after irradiation, which was accompanied by increased cellular proliferation. This situation reversed at higher doses (≥ 1 Gy) and points to the fundamental differences between low and high dose radiobiology. We have also examined the capability of combinations of low dose low LET irradiation (gamma rays and protons) to modulate the redox state and survival parameters in human and rodent neural stem and precursor cells. Significant data now indicates that the dose (and possibly dose rate) as well as the interval between multiple exposures is critical in dictating the magnitude and nature of the ensuing adaptive effects. Collectively, these data suggest that redox sensitive signaling may promote radioresistance.

To gauge the consequences of low dose irradiation on the intact CNS, WT mice were subjected to single or priming-challenge dosing paradigms and analyzed 1 month later. Immunostaining of tissue sections for resident (Iba1 positive) and activated (ED1 positive) microglial populations in the hippocampus were used to measure changes in neuroinflammation. Qualitative analyses of resident microglial populations did not show

major alterations in the number of Iba1 positive cells after any of the dosing paradigms. Quantification of Iba1 levels in various hippocampal regions (*i.e.* DG, DH, CA1 and CA3) is currently underway. Concurrent, analyses of activated microglia (ED1 positive) will be enumerated in each hippocampal region to further assess the inflammatory response after each dosing paradigm. Neurogenesis studies are also underway to assess the impact of low dose exposure on the maturation of neural stem cells, using standard dual-immunofluorescent labeling of proliferating stem/progenitor cells (BrdU positive) co-labeled with mature (NeuN) and immature (Tuj1) neuronal markers.

While the mechanisms regulating the responses of tissue-specific stem cells and their immediate progeny to low dose irradiation are certain to be complex, underlying themes are emerging that suggest changes in redox state are critical. Radiation-induced oxidative stress may prime stem cell pools and their microenvironmental niches for adaptive remodeling, changes that may hasten the recovery of irradiated normal tissue in the brain.

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