

Radioadaptation in Neural Stem Cells Exposed to Low Dose Irradiation

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In the CNS, irradiation of multipotent neural stem and precursor cells has been shown to cause a persistent oxidative stress that impacts radiosensitivity, mitochondrial function, and cell fate. The nature, magnitude and duration of reactive species dictates whether these radiation-induced changes are harmful or beneficial to a variety of *in vitro* and *in vivo* endpoints of viability and function. We have shown that acute low dose irradiation (2-10 cGy) can elicit significant increases in reactive oxygen (ROS) and nitrogen (RNS) species over several days post-exposure. These changes can be attenuated when the dose is protracted over several weeks using a ^{57}Co flood source having a surface dose rate of $\sim 1\text{cGy/day}$ or when split or fractionated dosing paradigms are used. Analysis of three different primary neural stem cells indicates that protracting the dose (5-20 cGy) affords increased cell survival from 5-20%. Enhancement of survival is also found when cells are primed with low dose irradiation, (2 or 10 cGy) and allowed to adapt for 1-2 days before being subjected to challenge doses in the range of 1-5 Gy. Enhanced survival is most often associated with lower oxidative stress levels, and increased antioxidant capacity, in terms of elevated MnSOD levels. Interestingly, in cells subjected to low dose or low dose rate exposures, radioadaptation also promoted DNA repair capacity, as the removal kinetics of gamma-H2AX foci was markedly faster, suggesting an enhanced repair of DNA DSBs.

We have also examined the capability of low doses and dose rates of proton irradiation to modulate the redox state in neural precursor cells. Alterations found in oxidative stress are also likely to underlie a certain fraction of the radioadaptation under these circumstances that protect these cells from higher additional challenge doses. Preliminary data suggests that the priming dose rate may be critical in dictating the magnitude and nature of the ensuing adaptive effects. These data suggest that increases in reactive species following low dose exposure can activate redox sensitive signaling to upregulate antioxidant defenses and promote radioresistance. 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. These changes are likely to prime stem cell pools for the adaptation and remodeling of the irradiated tissues in which they reside, and highlight the importance of understanding the interplay between stem cell niches and the redox microenvironment.