REGIONAL DIFFERENCES IN THE RESPONSE OF NEURAL STEM CELLS AND THEIR MICROENVIRONMENT TO IONIZING RADIATION

Akademisk avhandling

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av

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I. Hellström NA, Zachrisson O, Kuhn HG and Patrone C.
Rapid quantification of neurons and stem/progenitor cells in the adult mouse brain by flow cytometry
Letters in Drug Design and Discovery (2007) 4:532-39

II. Hellström NA, Björk-Eriksson T, Blomgren K and Kuhn HG.
Differential recovery of neural stem cells in the subventricular zone and dentate gyrus after ionizing radiation
Stem Cells (2009) 27:634-41

III. Hellström NA, Ståhlberg A, Swanpalmer J, Björk-Eriksson T, Blomgren K and Kuhn HG.
Unique gene expression patterns indicate microglial contribution to neural stem cell recovery following irradiation
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ABSTRACT

Radiation therapy is one of the most effective tools for treating malignant tumors; however, cranial irradiation often results in intellectual impairment and cognitive deficits, such as impaired learning and memory. Ionizing radiation generates DNA damage, causing proliferative cells to undergo apoptosis. In most brain regions, the generation of neurons is complete at birth. However, in two discrete regions, the granule cell layer of the hippocampus and the subventricular zone (SVZ) of the lateral ventricle, stem cell continuously proliferate and generate new neurons throughout life. Due to their high proliferative capacity, these cells are particularly vulnerable to ionizing radiation.

The studies in this thesis focused on the immediate and late effects of ionizing radiation on neural stem cells and their microenvironment. We found that a single dose of 6 Gy at postnatal day 9 leads to long-lasting decreases in both stem cell proliferation, as well as neurogenesis, in the adult rat. Even though the two stem cell regions were equally affected by the initial radiation, there was a differential response in stem cell recovery. While hippocampal stem cells were long-term affected; SVZ stem cells seemed to recover with time. In addition, the radiation injury caused an immediate inflammatory response in the postnatal brain, which was not sustained into adulthood. Interestingly, irradiated microglia in the SVZ, but not hippocampus, upregulated several genes coding for growth factors known to promote stem cell maintenance, proliferation and survival. The specific upregulation of these stem cell-related genes in irradiated SVZ microglia could potentially contribute to the recovery of the stem cell population seen in the SVZ, which was lacking in the hippocampus. Taken together, these data demonstrate the pronounced susceptibility of hippocampal stem cells to ionizing radiation, and highlight the importance of shielding this structure from irradiation to minimize functional consequences.

Key words: ionizing radiation, neurogenesis, neural stem cells, inflammation, microglia, stem cell niche, trophic support

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