Abstracts

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RADT-10. LITHIUM TREATMENT PROTECTS MICROGLIA AND NEWLY GENERATED NEURONAL POPULATIONS IN A MOUSE MODEL OF CRANIAL RADIOTHERAPY
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BACKGROUND: Radiotherapy remains a cornerstone of the treatment of high-grade brain tumors. However, while lifesaving, it results in long-term complications in 50-96% of the treated individuals, where cognitive deficits are particularly debilitating. Currently, no treatments or preventive strategies are available to avert these deficits. Lithium (Li), long used to treat bipolar affective disorder, has been shown to reduce radiation-induced cognitive deficits in rodent models by preventing apoptosis of the neuronal stem and progenitor cells in the hippocampus and stimulating their proliferation. This work aimed to further elucidate the mechanisms behind the protective and pro-regenerative actions of Li in the irradiated young brain.

METHODS: Postnatal day (PD) 21, C57BL/6j mice were injected intraperitoneally with Li chloride (4 mmol/kg) and kept on a Li carbonate-containing diet for 4 weeks. Control animals were injected with saline and administered an equivalent control diet. On PD 25, the animals were administered a single-dose whole-brain radiation of 8 Gy and were subsequently sacrificed at different time points, spanning from 2 weeks to 1 year. At sacrifice, the hippocampi were harvested for single-cell RNA sequencing using a novel, 2-step protocol to harvest viable cells of all types, including neurons. RESULTS: The results showed that radiation triggered the expression of senescence-related genes in the hippocampal microglia (e.g., Cdkn1a, Ccl12), which Li has prevented through the activation of the Bcl2 family of genes. Moreover, they corroborate the protective effect of Li on newly generated hippocampal neurons, which undergo remodeling over time, leading to the emergence of new subpopulations.

CONCLUSIONS: This work represents another advancement towards understanding the action of Li in the irradiated brain and confirms its potential to become the first pharmacological treatment for radiation-induced complications.