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TIME-SERIES SINGLE-CELL ANALYSES REVEAL INCESSANT RE-WIRING OF MICROGLIA AFTER CRANIAL IRRADIATION

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Cranial irradiation (IR) is one of the pillars of treatment of brain tumors and metastases, but it causes progressive neurocognitive impairments in cancer survivors. Neuroinflammation is believed to contribute to this, but its dynamics and consequences on brain function remain poorly understood. Here, we performed longitudinal molecular and cellular profiling of the irradiated mouse hippocampus, a key brain structure for cognitive tasks, using single cell transcriptomics and computational analyses, proteomics and histology, covering multiple time points, from 6 hours to 1 year after IR. We found that IR induced biphasic inflammatory waves, and microglia were the key orchestrating cells. The first wave occurred within the first 24 hours after IR, triggered by the death of neural progenitors in the dentate gyrus. The second, delayed wave occurred 2 weeks after IR, coupling interferon signaling to mitotic progression, and a subsequent induction of temporally regulated subtypes. Trajectory analysis uncovered that this subset of microglia drives microglial mitotic progression, cell death, or a senescent-like phenotype predominantly observed 6 weeks after IR. At this timepoint, the levels of cytokines known to have negative effects on cognition, like tumor necrosis factor and interleukin-6, were increased, coinciding with neuronal asynchrony of the hippocampal circuitry. We also found that IR caused progressive microglial loss and that they fail to repopulate the empty territories by self-renewal, leading to infiltration of peripheral macrophages to repopulate the hippocampus and differentiate into microglia-like cells by 6 months after IR. After 1 year, microglial alterations were largely related to neuronal and synaptic plasticity, and again coinciding with neuronal asynchrony. Thus, the inflammation profile in the hippocampus after IR is dynamic, and therapies targeting inflammation should be tailored accordingly.