Mapping Tumor-Induced Neuronal Hyperactivity in Glioblastoma Mouse Models

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor in human adults, with a median survival of approximately 15 months. Recent studies have demonstrated that glioma cells form functional synapses with neurons and that neuronal activity promotes tumor progression. Sun et al. (2025) used viral tracing to map the anatomical connectivity between neurons and patient-derived glioblastoma cells, identifying brain regions that send synaptic input to the tumor. This study extends this work by mapping neuronal hyperactivity across the brain in tumor-bearing mice using c-Fos immunohistochemistry. Immunocompromised mice received stereotactic injections of patient-derived glioblastoma organoids (UPO-10072) into the somatosensory cortex (n=10) or sham surgery with Hibernate A vehicle at the same coordinates (n=10). Open field testing was conducted at weeks 2 and 4 post-injection. Mice were perfused immediately following the week 4 behavioral session, and brain sections were processed for c-Fos and human nestin immunostaining. Automated cell quantification was performed using QuPath following alignment to the Allen Mouse Brain Atlas. Tumor-bearing mice showed no behavioral differences at week 2 but exhibited significantly reduced center time at week 4, indicating an anxiety-like phenotype. Brain-wide c-Fos mapping revealed region-specific changes, with the amygdala showing significantly increased c-Fos expression in tumor-bearing mice compared to controls. Most other quantified regions showed no significant differences between groups. Our findings indicate that GBM induces increased neuronal activity in the amygdala, which provides a potential neural correlate for tumor-associated anxiety-like behavior.