Targeting Pathological Neurotransmission Dynamics Through de novo Regulatory Modulation to Suppress Glioma Progression

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Glioma is an aggressive, life-threatening form of brain cancer with poor clinical outcomes. Despite decades of research, tumor-intrinsic mutations cannot explain disease progression alone. Current understanding and effective therapies are limited by the complex nature of the brain's surrounding microenvironment. This project aims to investigate neurotransmission dynamics as an upstream regulator of glioma progression and allow for efficient therapeutic strategy development. Synaptic vesicle fusion, driving timed release of transmitters, is tightly regulated by soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complexes. Native mass spectrometry was used to analyze the stoichiometry and conformation of SNARE regulatory assemblies under glioma conditions, revealing a novel redistribution toward fusion-permissive conformations with relative abundance increases of 1.4x–2.1 ($p < 0.01$). Further analysis of neuronal proteomic datasets demonstrated elevated tumor-supportive signaling through a 1.5x increase in neuroligin-3 under conditions of elevated synaptic activity ($p < 0.05$). Next, high-performance modeling found these distributions changed transmission kinetics from synchronous to sustained release. Finally, to explore therapeutic intervention, the design of de novo modulation targeting SNARE dysregulation revealed a binding affinity of -10.2 kcal/mol. Molecular dynamics simulations confirmed stability with an RMSD below 2.0 Å over 50–100 ns and a radius of gyration stabilized at ~2.9–3.0 nm. Overall, this project's findings connect glioma progression to synaptic dysregulation, directing effective therapeutic intervention.

Awards Won: