0.35 and 0.37, respectively). For example, a diagnosis of IDH-wildtype glioblastoma yielded median survivals varying from 289 days in patients with the signature of marked EGFR amplification, MGMT methylation, and histone mutations to 425 days in those with the signature of neuron-GBM interactions, histone and EGFR wild-types, and variable MGMT methylation. These findings suggest network-based analysis can reveal distinct signatures of survival with better prognostic fidelity than current gold standard diagnostic categories.

CNSC-27. AN IDO-PROTAC HIGHLIGHTS A NOVEL TRYPOTOPHAN METABOLISM-DEPENDENT ROLE FOR IMMUNOSUPPRESSIVE IDO IN HUMAN GliOBLASTOMA
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INTRODUCTION: Indoleamine 2,3-dioxygenase 1 (IDO) is an immunosuppressive enzyme that catalyzes the essential amino acid, tryptophan (Trp), into the metabolite, kynurenine. IDO is expressed in >90% of patient resected GBM. IDO suppresses the anti-brain tumor immune response, in-part, through non-metabolic activities. To determine how IDO regulates pathways that commonly regulate GBM immune response and antiprotein degradation (IDO-proteolysis targeting chimera; IDO-PROTAC) effects were studied in multiple human models of GBM.

METHODS: The expressing GBM cell lines, U87, U138, as well as the patient derived xenograft (PDX) GBM43, were treated with either IDO-PROTAC, an IDO enzyme inhibitor, or IDO siRNA, followed by RNA-seq analysis and/or mass spectrometry with quantitative proteomics using tandem mass tag (TMT) labelling. RESULTS: Transcriptomic analysis revealed differentially expressed genes that were commonly regulated after treatment with the IDO-PROTAC as compared to treatment with the mutant PROTAC or IDO enzyme inhibitor groups in U87, U138, and GBM43 cells. Mass spectrometry analysis found 34 unique proteins that were differentially expressed compared to GBM cells, with additional 20 unique proteins that were identified in the supramolecular of GBM cells after IDO-PROTAC treatment. Meta-analysis of the transcriptomic and proteomic analyses identified a novel factor that was unique to IDO-PROTAC treatment.

CONCLUSIONS: This study discovered multiple new targets and pathways that immunosuppressive IDO regulates through a non-metabolic function. Functional analyses that validate the newly-discovered IDO-dependent, IDO-enzyme independent factors, are ongoing.

CNSC-28. IDENTIFICATION OF EA2-KV12 POTASSIUM CHANNEL COMPLEX IN NEURON-GBM COMMUNICATION REVEALS GBM VULNERABILITY TO DESIGNER INTERFERENCE PEPTIDE
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Glioblastomas (GBMs) are the most aggressive brain tumors. GBM cells form extensive tumoral networks to communicate with other cells and to connect with surrounding neurons. Neuronal activity promotes GBM cell proliferation by secreting pro-tumorigenic factors and triggering neuronal-activity-dependent Ca2+ transients, which are persisted and transmitted via tumor networks to promote overall tumor growth and therapy resistance. While how these processes are regulated is largely unknown, here we show the GBM networks and Ca2+ transients are regulated by a voltage-gated potassium channel complex composed of EA2 and Kv2.12.2. Comparing EA2-Kv2.12 to a control, we find that EA2-Kv2.12 forms a functional channel of Glutamate receptor expressed in the context of tumor cell and astrocyte contact. Here, we exploited the concept of tumor networks to heterogeneous connectivity with the glial microenvironment. Using high-resolution light microscopy, ultrastructural tissue imaging, patch-clamp electrophysiology, intravital structural and functional microscopy, we characterized tumor-astrocyte communications. More specifically, we found that the EA2-Kv2.12 channel is associated with DA signaling and attenuates GBM growth andvasculogenesis. We therefore used our tool to demonstrate that targeting neuronal EA2-Kv2.12 channel could be a potential therapeutic strategy for GBM.

CNSC-29. INVESTIGATING THE INFLUENCE OF DOPAMINERGIC ACTIVITY ON THE GliOBLASTOMA NICHE
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Glioblastoma (GBM) is an incurable disease of adults and children, and the deadliest form of central nervous system (CNS) malignancy. Despite major advances in our understanding of GBM biology in recent years, the prognosis for patients who develop this disease has not improved. If we hope to find new treatments for GBM that are safe and effective, we desperately need to reframe our thinking. The brain’s chemical milieu is rich with neurotransmitters, and our lab’s screen of 680 neuroactive compounds on patient-derived glioblastoma stem cells (GSCs) in vitro strongly implicates neurotransmitter pathways as critical regulators of the GSC niche. More specifically, disrupting dopamine signaling by inhibiting its receptor D4 on GSCs reduces their growth and sensitizes GBM to the proliferative effects of the anti-cancer reagents. In vivo (Dolma et al., Cancer Cell, 2016). Dopamine (DA) is a catecholamine neurotransmitter that is essential for reward learning and movement and has numerous roles in cognition. Consequently, disruption of DA signaling is associated with a diversity of brain diseases ranging from drug addiction to schizophrenia to Parkinson’s. Our research aims to determine how DA signaling affects normal neural stem cell (NSC) and tumorigenic GSC populations, as we hypothesize that GSCs arising/residing in DA projection zones (not dopaminergic (DAergic) activity for GBM growth. Toward these aims, we have developed in vitro model systems and harnessed them to study NSC and GSC niches in the context of either controlled activation or deletion of DAergic neurons. These manipulations of the brain’s DAergic neurons are well understood, with its therapeutic capability, genetic deletion, and neurotransmitter-mediated ablation in mice. Ultimately, unraveling the dopaminergic influence on GBM could contribute to a rethinking of existing treatments—that modulate DA signaling and are already approved to treat CNS disorders—to patients with this deadly brain cancer.

CNSC-30. IN VIVO DYNAMICS OF ASTROCYTE-GliOBLASTOMA TUMOR NETWORKS
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As one of the most aggressive incurring primary brain tumors, glioblastomas show a high invasiveness and therapeutically resistance caused by their cellular and molecular heterogeneity. In previous studies, we showed that glioma cells interconnect using membrane protrusions called tumor microtubes to form a therapy-resistant malignant network. Here, we extend the concept of tumor networks to heterogeneous connectivity with the glial microenvironment. Using high-resolution light microscopy, ultrastructural tissue imaging, patch-clamp electrophysiology, intravital structural and functional microscopy, we characterize tumor-astrocyte communications. More specifically, we found that the EA2-Kv2.12 channel is associated with DA signaling and attenuates GBM growth andvasculogenesis. We therefore used our tool to demonstrate that targeting neuronal EA2-Kv2.12 channel could be a potential therapeutic strategy for GBM.