LGG-54. ASTHMA REDUCES GLIOMA FORMATION BY T CELL DECORIN-MEDIATED INHIBITION OF MICROGLIA

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To elucidate the mechanisms underlying the reduced incidence of brain tumors in children with Neurofibromatosis type 1 (NF1) and asthma, we leverage optic pathway glioma (*Nf1*-OPG) mice, human and mouse RNAseq data, and two different experimental asthma models. Following ovalbumin or house dust mite asthma induction at 4-6 weeks of age (WOA), *Nf1*-OPG mouse optic nerve volumes and proliferation are decreased at 12 and 24 WOA, indicating no tumor development. This inhibition is accompanied by reduced expression of the microglia-produced optic glioma mitogen, Ccl5. Human and murine T cell transcriptome analyses reveal that inhibition of microglia Ccl5 production results from increased T cell expression of decorin, which blocks Ccl4-mediated microglia Ccl5 expression through reduced microglia NFκB signaling. Decorin or NFkB inhibitor treatment of *Nf1*-OPG mice at 4-6 WOA inhibits tumor formation at 12 WOA, thus establishing a potential mechanistic etiology for the attenuated glioma incidence observed in children with asthma.

LGG-55. AUTOPHAGY SENSITIZES CNS TUMORS TO TARGETED THERAPY BY LOWERING THEIR APOPTOTIC THRESHOLD

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Autophagy inhibition improves the effectiveness and overcomes RAF pathway inhibition (RAFi) resistance across multiple CNS tumors and molecularly distinct resistance mechanisms. Mechanistic links between autophagy and apoptotic cell death may explain this ability to improve RAFi response and reverse resistance. RAFi sensitive (MAF 794, AM38) and resistant (MAF 794R, MAF 905-3, AM38R, B76) BRAFV600E CNS tumor cell lines were analyzed at baseline, following RAFi (vemurafenib), autophagy inhibition (chloroquine or shRNAs), and combination therapy. Growth assays and caspase activation were monitored by Incucyte Zoom. qRT-PCR evaluated key pro-apoptotic BH3-only members of the BCL-2 family. Broad BH-3 profiling was completed using the Letai JC-1 Plate-Based protocol. Western blot analysis assessed protein levels. Combination pharmacologic treatment caused alterations in key pro-apoptotic BH3-only proteins including an increase in BNIP3L and PUMA. Genetically inhibiting autophagy with shRNAs for ATG5 and ATG7 (proteins required for formation of the autophagosome) produced similar results with increases in both protein and mRNA levels of BNIP3L and PUMA following RAFi treatment. This suggested autophagy-mediated regulation of BH3 proteins functions to determine cellular apoptotic threshold. Caspase activation demonstrated increased effectiveness of combined RAFi and autophagy inhibition overcoming the apoptotic threshold compared to single drug treatment. BH3 profiling demonstrated a dependence on BCL-2 to inhibit apoptosis. BH3 mimetics competitively bind to pro-survival BCL-2 family members, blocking their protective effects and pushing tumor cells towards apoptosis. Autophagy inhibition can also improve treatment response by overcoming the apoptotic threshold in RAFi resistant cells and magnifying the apoptotic response in sensitive cells. BH3 profiling reveals CNS BRAFV600E are BCL-2 dependent cells, unprimed for apoptosis, which may be good candidates for additional treatment with BH3 mimetics such as venetoclax. This presents an attractive treatment for MAPK activated CNS tumors by enhancing apoptotic cell death by targeting the MAPK pathway, autophagy and BH3.

LGG-56. SURGICAL MANAGEMENT OF PRE-CHIASMATIC INTRAORBITAL OPTIC NERVE GLIOMAS IN CHILDREN AFTER LOSS OF VISUAL FUNCTION – RESECTION FROM BULBUS TO CHIASM

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INTRODUCTION: Optic pathway gliomas (OPG) in children carry significant morbidity and therapeutic challenges. The subgroup of pre-chiasmatic gliomas manifest with exopthalmus are a subgroup where, after blindness has occurred, an intraorbital and intradural resection is a curative option. We present a two-center cohort using two different surgical approaches and describe indication, technique, and long term surgical outcome. METHODS: A retrospective analysis in both centers was performed to included patients < 18 years at diagnosis with a pre-chiasmatic intra-orbital glioma, in whom a resection from the bulb to the chiasm was performed. RESULTS: 11 patients were included. 4 had NF1. Mean age at surgery was 7.0 years. Interval between diagnosis and surgery was 1-74 (median 10) months. Two had prior chemotherapy, one radiation, one both, one prior intraorbital surgery. In all 5 progression occurred. Indications for surgery were exophthalmos, pain, tumor progression or a combination. 8 patients (Group A) underwent an extradural trans-orbital-roof approach to resect intra-orbital tumour including the optic canal part plus intradural pre-chiasmatic resection. In 3 patients (Group B) a combined supra-orbital mini-craniotomy plus orbital frame osteotomy was used for intraorbital tumour-resection, excluding the optic canal part, plus intradural pre-chiasmatic resection. GTR was achieved in 7/8 of Group A and none had a recurrence (mean-FU 42 month). One residual behind the bulbus showed progression, treated by chemotherapy. All residuals in Group B were remnants of the optic nerve within optic canal remained stable (mean FU 11.8 months). No patient had a chiasmatic functional affection or permanent oculomotor deficits. Two after prior radiotherapy developed slight enophthalmos. CONCLUSION: In these selected patients surgical resection from bulb to chiasm (± removal of optic canal tumor) is safe without long-term sequela and with excellent cosmetic result. Surgery removes immediately exophthalmos and provides an effective long-term tumor control. It should be considered therapy of choice.

LGG-58. UNDERSTANDING THE TRANSCRIPTIONAL HETEROGENEITY OF PEDIATRIC LOW-GRADE GLIOMAS AND ITS IMPLICATION FOR TUMOR PATHOPHYSIOLOGY

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Pediatric low-grade gliomas (pLGGs) are the most frequent brain tumors in children and comprise a heterogeneous group of tumors with different locations, histologic subtypes, ages at presentation, and clinical behavior. Tumors frequently respond to treatment with chemotherapy or surgical removal, but they can regrow after a period of quiescence, requiring further therapy. Thus, a deeper understanding of the molecular processes involved in these tumors is required to develop therapeutic strategies that are effective against their disease mechanisms. To better understand the cellular behaviors of this heterogenous group of tumors, we have employed single-cell and single-nuclei RNA sequencing technologies to analyze a large-scale dataset (>250,000 cells) of pLGGs. Analysis of this data identified a heterogenous population of cell types and cell states, detecting mature and progenitor-like astrocytes and oligodendrocytes, as well as cells exhibiting senescence or cycling programs. Moreover, we identify a significant immune infiltrate, comprised primarily of microglia. In addition to heterogeneity within pLGG tumors, heterogeneity between LGG subtypes represents another layer that stratifies pLGG biology. We performed a compositional analysis of the cell types present in these tumors and compared transcription signatures and gene expression programs across shared cellular populations of histologically and genetically distinct pLGGs. Finally, we optimized our