ECOA-9. INTEGRATION OF MOLECULAR AND METHYLATION CLASSIFICATIONS YIELDS THREE MENINGIOMA GROUPS AND SUGGESTS CHROMOSOME 1P LOSS MAY BE CRITICAL TO THE AGGRESSIVE GROUP

James Bayley[1], Caroline Hadley[1], Arif Harmanci[2], Akdes Harmanci[1], Tiemo Klisch[1], Akash Patel[1]; [1]Baylor College of Medicine, Houston, TX, USA. [2]University of Texas Health Sciences Center at Houston, Houston, TX, USA

Next-generation sequencing has deepened our understanding of meningiomas, particularly those that behave aggressively. Classifications using either DNA methylation profiling or RNA-sequencing predict tumor behavior more reliably than WHO grade, and segregate common meningioma features similarly, implying possible overlap between classifications. In this study, we performed DNA methylation profiling, RNA-sequencing, and whole-exome sequencing on 110 primary meningiomas (90 WHO I, 20 WHO II). Unsupervised non-negative matrix factorization demonstrated three epigenetic types which were highly concordant with our published transcriptional types (87.3% concordance). Two additional classifications (one using 1p/22 loss, the other merlin expression/chromosomal instability) were also highly concordant and an overall meningioma group (MenG) classification was assigned integrating all four together. MenG A and B rarely recur, while MenG C behave aggressively (median recurrence free survival (RFS) of 3.1 years), even after gross total resection (median RFS 4.2 years). MenG A tumors retain Merlin expression (no chromosome loss or NF2 mutation) and harbor mutations in TRAF7, AKT1, or KLF4. Both MenG B and C are merlin-deficient, but MenG B demonstrate low rates of CNV and MenG C high rates of CNV, particularly loss of chromosome 1p. Using partial least squares regression (PLS), we explored how gene expression correlated with promoter methylation and CNV, thereby classifying genes which correlated closely as 'methylation-driven' or 'CNV-driven'. Overall, there were more methylation-driven (5.7%) than CNV-driven (2.9%) genes. Differentially expressed genes (DEGs) were enriched for both methylation- and CNV-driven genes at similar proportions (10.6% and 5.8%), but DEGs unique to MenG C were significantly enriched for CNV-driven (23.7%), but not methylation-driven (4.7%) genes, primarily due many MenG C DEGs on chromosome 1p. Overall, this work suggests three underlying meningioma groups which are identifiable through methylation, transcriptional, or genetic/cytogenetic profiling and warrants exploration of the role of chromosome 1p in group that behaves aggressively.

ECOA-10. INTEGRATED GENOMIC AND CLINICAL ANALYSIS OF BRAF-MUTATED GLIOMA IN ADULTS

Pinky Langat[1,2], Taibo Li[3], Wenya Linda Bi[1,2], Karisa C. Schreck[3]; [1]Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [2]Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA. [3]Department of Neuro-Oncology, Johns Hopkins Medical School, Baltimore, MD, USA

BRAF alterations are recognized as a significant driver of disease in pediatric low-grade glioma (pLGG) but the implications of *BRAF* alterations on the natural history and response to treatment are unclear in adult glioma. We characterized the molecular and clinical features of a multi-institutional cohort of adults with *BRAF*-mutated gliomas. We identified patients with glioma containing *BRAF* alterations on sequencing in multi-institutional cohorts (Dana-Farber/Brigham Cancer Center, Johns Hopkins Hospital, GENIE, TCGA). *BRAF* alterations were grouped into previously defined classes: I (V600E; RAS-independent/dimerization-independent), II (RAS-independent/dimerization-dependent), III (RAS-dependent/dimerization-dependent) in addition to *BRAF* copy number gains, fusions, and other. We interrogated 289 *BRAF*-altered gliomas (199 patients >=18yrs, 90 patients <18yrs; range 0-85yrs), and observed histopathologic and molecular differences between *BRAF*-altered gliomas in adults versus pediatric patients. Amongst adults, the most common *BRAF* alterations were Class I followed by copy number gains, with glioblastoma (GBM) the most prevalent histology. In comparison, pediatric gliomas in our cohort frequently harbored Class I mutations followed by *BRAF* fusions, with primarily pilocytic astrocytoma and pLGG histologies. Principal component analysis and correlation analysis revealed molecular features associated with gliomas of different *BRAF* alterations and histologies, including mutation of *NF1*, a negative regulator of RAS, which was significantly associated with class II/III *BRAF* alterations (64.3%) and not observed in *BRAFV600E*-mutated gliomas (0%, n=62) ($p<0.0001$). Demographic and molecular features were evaluated for correlates for adult glioma risk stratification. Comparative survival analysis showed no significant difference between adult GBM harboring Class I compared to other *BRAF* alterations, whereas young adult age (18-35yrs) was associated with improved outcomes ($p<0.05$). Among 86 GBM patients with detailed clinicopathologic data, 7 received RAF-targeted therapy, with variable clinical response. This cohort of *BRAF*-altered adult gliomas demonstrates a broad range of molecular alterations with implications for treatment sensitivity and patient risk stratification.

FINAL CATEGORY: MULTI-OMICS

MOMC-1. EMPLOYING THE ZIKA VIRUS TO KILL PAEDIATRIC NERVOUS SYSTEM TUMOUR CELLS

Matthew Sherwood[1], Robert Ewing[1], Carolini Kaid[2], Thiago Giove Mitsugi[2], Keith Okamoto[2]; [1]University of Southampton, Southampton, UK. [2]University of Sao Paulo, Sao Paulo, Brazil

Malignant paediatric nervous system tumours, such as Medulloblastoma, Neuroblastoma and ATRT commonly harbour tumour cells with stem-like features which are highly tumorigenic and resistant to conventional cancer therapies. These tumours can exhibit high lethality and may result in severe sequelae, including cognitive and motor deficits that significantly affect patients' quality of life. Oncolytic virotherapy is a novel therapy class that exploits viruses that preferentially infect and destroy tumour cells. These viruses present a unique advantage in targeting highly heterogeneous cancers, such as nervous system tumours, as they possess a secondary mechanism of action through which they induce a tumour-specific immune response. Clinical studies employing oncolytic virotherapy have in general reported low toxicity and minimal adverse effects, deeming oncolytic virotherapy as a potentially attractive and safer intervention against paediatric tumours. The Zika virus (ZIKV) is capable of infecting and destroying neural stem-like cancer cells from human embryonal Central Nervous System (CNS) tumours in vitro and in vivo. Infection of CNS tumour cells with ZIKV effectively inhibits tumour metastasis in mice and, in some cases, induces complete tumour remission. Neuroblastoma arises from immature nerve cells and multiple Neuroblastoma cell lines are susceptible to ZIKV infection and oncolysis. These initial findings have demonstrated the potential for a ZIKV-based virotherapy against paediatric nervous system tumours and warrants examination into the molecular mechanisms through which ZIKV executes its oncolytic ability. My research goal is to elucidate the mechanisms which are of paramount importance for ZIKV-induced oncolysis of brain tumour and Neuroblastoma cells. Utilising global expression omics profiling of ZIKV infection and mapping of viral protein-host protein interactions will identify these mechanisms both at the cellular pathway and molecular levels. These collectively will inform our understanding of how we can employ a future ZIKV-based virotherapy against paediatric nervous system tumours.

MOMC-2. GLIOBLASTOMA METABOLIC SYMBIOSIS: WHEN LACTATE TAKES THE LEAD.

Joris Guyon[1,2], Claire Larrieu[2], Cyrielle Bouchez[2], Ignacio Fernandez Moncada[2], Aurelien Coffe[2], Macha Nikolski[2], Andreas Bikfalvi[1], Thomas Daubon[2]; [1]INSERM U1029, Bordeaux, France. [2]CNRS UMR5095, Bordeaux, France

Glioblastoma (GBM) is a common and devastating brain tumor, associated with a low median survival, despite standard therapeutic management. Among its major features, GBMs are highly angiogenic and exhibit paradoxically an elevated glycolysis. Most of differentiated cells convert glucose into pyruvate that enters into the Krebs cycle to maximize energy production in the presence of oxygen. For cancer cells, glucose uptake and catabolism are increased regardless of oxygen level. However, their energy needs are important – mainly for rapid growth – that it requires a much faster production flow. It is at this step that lactate dehydrogenase (LDH) are involved: LDHA converts efficiently pyruvate into lactate and generates NAD^+ to maintain glycolysis. Thus, the lactate formed is exported into the extracellular compartment inducing an unfavourable acidification of the microenvironment. Moreover, LDHB, another LDH isoform, metabolizes lactate into pyruvate for generating energy in mitochondria. Though LDHA has already been studied in many cancers including GBM, the simultaneous role of LDH enzymes have not yet been investigated in GBM development. Hypoxia-driven LDHA expression and lactate production increased cell invasion. Infusing 13C-lactate in starved cells rescued TCA cycle. Then, we showed that, under hypoxia, double sgLDHA/B cell growth and invasion was dramatically decreased in comparison to control cells, mainly caused by an increase in apoptosis. Moreover, double impairment of LDHA and B significantly reduced tumor growth and cell invasion, and induces a massive increase in mouse survival. Tracing experiments with 13C-Glucose coupled with RNA sequencing revealed how metabolism adapts to these contraints, by modifying electron transport chain subunit expressions or by increasing lipid droplet formation. Considered for a long time as a metabolic waste, lactate is shown here to play a critical role in GBM cell symbiosis. This study highlighted GBM adaptability through the LDH isoforms and their involvement in GBM development.