PATH-61. IMMUNOHISTOCHEMICAL PHENOTYPING AND SURVIVAL ANALYSIS OF WHO GRADE II-IV GLIOMAS
Nora Poulou, Srikrishna Satizatru, Charles Opalak, Mikhail Dozmorov, Jason Harrison, Richard, and William Broadaw, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

INTRODUCTION: Specific genetic mutations are linked to clinical prognosis in gliomas. There has been a recent growing demand to understand the association between tissue biomarker expression and survival. Using patient-derived samples, WHO grade II-IV gliomas were evaluated by the protein-staining pattern of molecular markers of interest across tumor grade, and the association between their expression and survival was investigated.

METHODS: Tissue microarrays (TMA) containing duplicate 1 mm cores were generated from 78 gliomas (WHO grade II-IV) using an automated TMA system. Immunohistochemistry was performed per the manufactures recommendation to evaluate expression of: Wilms tumor 1 (WT1), platelet endothelial cell adhesion molecule (CD31), adhesion G protein-coupled receptor ES (CD97), complement decay-accelerating factor (CD55), hypoxia inducible factor 1 subunit alpha (HIF1α), EGF-like module-containing mucin-like, heparin sulfate proteoglycan receptor-like 5 (EPHRE5), hydrogenase 1 (IDH1). Samples with moderate (+1) or intense (+2) staining for WT1, CD31, CD97, or HIF1α, or any staining to EMR3 or IDH1 mutation, were considered positive. RESULTS: Of the 78 tumor samples, there were 11 (14%) WHO grade II, 22 (28%) grade III, and 45 (59%) grade IV gliomas. Across grade III gliomas, anaplastic astrocytomas had significantly higher positive WT1 (p=0.04), CD31 (p=0.002) and IDH1 wild-type (p<0.0001) staining. High-grade (III & IV) gliomas had significantly higher positive staining for WT1 (p=0.013), CD31 (p=0.024), integrin (p=0.026), and EGF-like module-containing mucin-like, heparin sulfate proteoglycan receptor-like 5 (EPHRE5) in wild type (p=0.004) staining for WT1 (p=0.0001), CD31 (p=0.009), CD97 (p=0.024), EMR3 (p=0.036), and IDH1 wild type (p=0.006) were associated with worse overall survival. After adjusting for patient age, positive staining for WT1 (p=0.003) was associated with a worse overall survival. Among patient-derived samples, an immunohistochemistry, unique biomarker staining patterns were identified for WHO grade III anaplastic astrocytomas and for high-grade gliomas. Irrespective of grade, staining for WT1, CD97, CD31, EMR3, and IDH1 wild-type were associated with worse overall survival.

PATH-62. QUANTITATIVE ANALYSIS OF ASSOCIATED-AGM METHYLATION IN NEWLY MALIGNATED GBLOBLASTOMA
Addison Barnett,1 Anas Saeed Bamashmos1, Hong Li1, David Bosler1, Justin Lathia2, Gabrielle Yeane1, Asad Ali1, Sooyna Sagar1, Alirea Mohammadi1, Glen Stevens1, Lulyana Angelov2, Diane Barnett1, and Mineette Alhuwalia1,1 Cleveland Clinic, Cleveland, OH, USA, 2Cleveland Clinic Lerner Research Institute, Cleveland, OH, USA, 3Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA

INTRODUCTION: Glioblastoma (GBM) and MGMT have been reported to have sexual dimorphism. In multiple studies, including our own population-based cohort analysis, females had higher rates of MGMT methylation and improved methylation-associated progression-free and overall survival outcomes compared to males. MGMT methylation is assessed as a mean of five cystine-phosphate-guanine (CpG-5) islands (CpG methylation is highly inversely correlated with MGMT RNA expression). The geometric mean of this high grade glioma (HGG) dataset showed that female patients had significantly higher rates of mean methylation compared to males (14.0 vs 9.0%, p=0.019). Females also had higher rates of age disseminated demyelinitis (ADD). She was treated with intravenous methylprednisolone followed by oral prednisone with resulting clinical and radiographic improvement. She was re-admitted to hospital 4 months later with encaphalopathy. Imaging showed a new enhancing mass in the pericallosal frontal lobes. Repeat brain biopsy showed diffuse large B-cell lymphoma. This case illustrates a highly unusual situation of biopsy-proven central demyelination preceding a primary CNS lymphoma diagnosis. It raises a number of etiopathological questions concerning the coexistence and potential causal relationships between demyelination and lymphoma. Additionally, it highlights the need for repeat biopsy if clinical and radiographic suspicion for lymphoma persists despite an alternative initial biopsy result.

PATH-63. TRANSCRIPTIONAL SIGNATURES IN HISTOLOGIC STRUCTURES WITHIN GLIOBLASTOMA TUMORS MAY PREDICT PERSONALIZED TREATMENT SENSITIVITIES AND SURVIVAL
Cymon Korsch1, Cheryl Claunch1, Prakash Ambady1, Emlar Bucher2, Daniel Schwartz2, Ramon Barajas3, Jeffrey Iffii4, Laura Heiser1, Leslie Muldowney1, and Edward Neuhaus1, Oregon Health & Science University, Portland, OR, USA, 1University of Washington, Seattle, WA, USA

OBJECTIVE: Personalized treatment strategies in Glioblastoma multiforme (GBM) has been hampered by intra-tumoral heterogeneity. The goals of this study were (1) to determine the impact of intra-tumoral heterogeneity on established predictive and prognostic transcriptional signatures in human GBM, and (2) develop methods to mitigate the impact of tissue heterogeneity on transcription-based patient stratification. METHODS: We analyzed transcriptional profiles of GBM histological structures from the open-source Ivy Glioblastoma Atlas Project. To generate these data, infiltrative tumor, leading edge, cellular tumor (CT), perinecrotic zones, pseudopalisading cells, hyperplastic blood vessels and microvascular proliferation from the same sample were isolated and underwent RNA sequencing. Data from The Cancer Genome Atlas were used for validation. Principle component analysis, network analysis and gene set enrichment analysis were used to probe gene expression patterns. RESULTS: Distinct biological themes were identified, with different tissue biomarker expression profiles. Classification of patients into GBM molecular subtypes varied based on the structure assessed, with many patients classified as every subtype depending on the structure analyzed. Using only CT to classify subtypes, we identified biologically similar patterns suggesting that biological and mesenchymal tumors may be more sensitive to chemotherapy and immunotherapy, respectively. Survival outcome predicted by an established multigene panel was confounded by histologic structure. Utilizing CT transcriptionomics we developed a novel survival prediction gene signature that identified the high risk group of patients in all gliomas, providing powerful CT tissue gene expression profiles. CONCLUSIONS: Histologic structures contribute to intra-tumoral heterogeneity in GBM. Using mixed-structure biopsy samples could incorrectly subtype tumors and produce invalid patient stratification using transcriptional analysis. This study suggests that new survival prediction gene signature that appears accurate even in mixed tissue samples. The biological patterns uncovered in the subtypes and risk-stratified groups have important implications for guiding the development of precision medicine in GBM.

PATH-64. PROSPECTIVE, BLINDED PLASMA BASED ANALYSES FOR DIAGNOSIS OF NEWLY DIAGNOSED GLIOBLASTOMA
Jane Lee1, Lisa Scarpace1, Rachel Hunt1, Kevin Nelson1, Darshana Patil2, Vineet Datta1, Dadasheb Akolkar3, Sachin Apurva2, Pooja Fulmali2, Shena Puranik1, James Snyder1, Houshan Noushmem4, Pradeep Devhare3, Ana deCarvalho5, Rajan Dattar6, Tobias Walther7, and Steven Kalkhan3,1 Henry Ford Health System, Detroit, MI, USA, 2Datar Genetics, Nashik, India, 3Henry Ford Hospital, Detroit, MI, USA

INTRODUCTION: In patients with newly diagnosed intracerebral lesions, gliomas are often suspected. However, other conditions such as multiple sclerosis, abscess or lymphoma are possible, as well. Furthermore, biopsy can be challenging due to eloquent and/or deep location within the brain. In this prospective, blinded study, analysis of plasma isolated cell-free DNA and exosome mRNA and miRNA from newly diagnosed glioma patients and from cancer-free volunteers was used to predict disease. METHODS: Plasma was drawn from 52 patients with newly diagnosed glioma (18 high grade glioma (HGG) and 34 low grade glioma (LGG)) and 14 participants without documented history of cancer and recent MRI brain which was negative for brain tumor. High quality DNA and RNA was isolated and sequenced using Next Generation Sequencing and Digital Droplet PCR was used for detection and verification of trace molecular artifacts. Multianalyte processing yielded data that was harmonized and interpreted through an
PATH-65. MOLECULAR SIGNATURE OF FAT1 RELATED MOLECULES IN GLIOMAS IN THE CONTEXT OF THE WHO 2016 CLASSIFICATION

Kumuzang Choudhury, Manvi Arora, Nargo Malik, Prerana Jha, Jyotuna Singh, Ashish Sur, Subrata Senha, and Vanshali Sah. All India Institute of Medical Sciences, Delhi, India

Glioblastoma (GBM, WHO grade-IV) being the most malignant and aggressive form of glioma remains a major clinical challenge, with an overall 5-year survival rate of only 9.8%. Till recently, glioma diagnosis and grading were solely dependent on the phenotypic and histological features. However, with the advancement in the understanding of the molecular biology of glioma, it has become clear that gliomas have been revealed to be genetically and functionally heterogeneous. The importance of these molecular/genotypic features of the tumor became evident by the inclusion of these molecular features by World Health Organization (WHO) in 2016 in glioma sub-grouping. Our lab is focused on studying the role of FAT1 gene, which is known to have a role in Drosophila tumor-suppressor gene, in glioma biology and aggressiveness. We observed FAT1 gene to have an oncogenic role in glioma where it has been found to upregulate migration/invasion, inflammatory microenvironment of the tumors, HIF1α expression/activity in glioma and to sensitize oncoplastic tumors under hypoxia and in regulating EMT/tumorigenic properties of GBM-cells under hypoxia. Here, we have characterized the molecular relationship between FAT1 related molecules and known molecular markers of glioma with the hope of identifying glioma subgroup with a specific molecular clinical significance by (i) analyzing the expression correlation of FAT1 and FAT1 regulated pro-inflammatory molecules like COX2, IL1b and IL6 with the known molecular markers of glioma like p53, IDH1, MGMT, EGFR, TERT in low-grade (grade-II) and high-grade (grade-III/IV) gliomas by real-time PCR, sequencing, immunohistochemistry and in-silico analysis of TCGA-GBM data (ii) Analyzing the regulatory role of FAT1 on the above known markers by siRNA mediated knockdown of FAT1 in in-vitro cell culture-system and (iii) further analyzed the identified molecular signature for their correlation with the patients prognosis/survival in a follow up in patients. We observed a novel molecular signature that has significance in correlation with patients’ clinical outcome. Therapeutic targeting of FAT1 may benefit patients with high FAT1 expressing tumors.

PATH-66. THE GENOMIC LANDSCAPE OF SPINAL CORD EPENDYOMA

Biswaarthan Ramani, Javier Villanueva-Meyer, Christine Gastlounbury, Jac Ee Mervyn, Kyle Walsh, Jennifer Taylor, Kathleen van Zutphen, Courtney Ondera, James Grenet, Andrew Bollen, Arie Perry, Tarik Tihan, David Solomon, and Melike Pekmezci.1 University of California San Francisco, San Francisco, CA, USA, 2University of Wisconsin, Madison, WI, USA, 3Duke University School of Medicine, Durham, NC, USA, 4Division of Neuro-Oncology UCSF, San Francisco, CA, USA

INTRODUCTION: Ependymomas are seen throughout the neural axis but spinal cord is most common in adults. A subset arises in the setting of congenital anomalies and is the spectrum of cooperating genetic alterations. METHODS: We performed targeted next-generation sequencing (NGS) to assess mutations, rearrangements, and chromosomal copy number alterations in 46 adult spinal cord ependymomas. RESULTS: The 24 females and 22 males ranged from 20-73 (median 46) years of age. Tumors were in the cervical (n=24), thoracic (n=12), and lumbar (n=10) spinal cord. Nine tumors (20%) harbored truncating NF2 mutations with loss of the remaining wildtype allele, with frequent monosomy 13q. Thirteen NF2-wildtype tumors (28%) showed monosomy 22q with frequent monosomy 13q and trisomy 7, 9, and 12. Seventeen tumors (37%) carried a near-tetraploid genome, likely due to genomic reduplication with frequent preservation of diploidy in chromosomes 13q (77%), 14q (88%), 21q (53%) and 22q (63%). Remaining cases did not show a recurrent pattern, but one harbored high-level MYCN amplification. Three of the six recurrences were seen in the last subgroup; however, there was no significant difference for progression-free survival between subgroups. None of the NF2-mutant tumors were in lumbar spinal cord, but there was no difference for tumor location or patient age between four subgroups. RESULTS: Three of the six recurrences were correctigraded. Of the 14 normal controls, 6 were concluded to be cancer-free. IDH1, EGFRVIII, and TP53 mutation had concordance of 64% (21/33), 88% (24/27) and 97% (28/29), respectively. CONCLUSION: For glioma, there is no specific correlation with patients’ clinical outcome. Therapeutic targeting of FAT1 in ependymoma may benefit patients with high FAT1 expressing tumors.

PATH-67. RECOMBINANT INTERLEUKIN-7 ENHANCES THE ANTI-TUMOR IMMUNITY OF A DENDRITIC CELL VACCINE IN A MURINE MALIGNANT GLIOMA

Sol Hyoung Oh1, Stephen Ahn2, Jae Sung Park1, Yong Kil Hong1, and Sang Eun Jeon1. 1St. Mary’s Hospital of Catholic University of Korea, Seoul, Republic of Korea, 2Department of Neurosurgery, The Catholic University of Korea, Seoul, Republic of Korea

BACKGROUND: Dendritic cell (DC)-based vaccines have been suggested as one of the promising immunotherapies for treating various cancers, including glioblastoma. We already developed a novel vaccination protocol with peptide-loaded DCs followed by a mixture of synthetic peptides, polynosinic-polycytidylic acid (poly-IC) and anti-CD40 antibodies (Trivax) in a melanoma mouse model. However, in a glioma mouse model, therapeutic efficacy is not as much as enough maybe due to relatively low antigens in glioma and blood brain barrier. MATERIAL AND METHODS: IL-7, which is one of the most important cytokines to expand and develop T cells with anti-tumor immunity, was co-administrated intravenously with Trivax in an orthotopic murine malignant glioma. RESULTS: Co-administration of IL-7 and Trivax significantly enhanced tumor regressor gene, an orthotopic murine malignant glioma. RESULTS: Co-administration of IL-7 and Trivax significantly enhanced tumor regressor gene.