Title

EPCO-25. AN IMMUNOMETHYLOMIC PLATFORM INTEGRATING SYSTEMIC IMMUNE PROFILES AND EPIGENETIC AGE IN NEURO-ONCOLOGY

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EPCO-22. IDENTIFYING NEOANTIGENS FOR A PERSONALIZED MUTATION-DERIVED GENOMIC VACCINE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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BACKGROUND: Glioblastomas (GBM) are known for having a lower mutational burden than many other tumor types. Nevertheless, somatic variants that occur in GBM mutational processes may give rise to neoantigens, which can be targeted in a personalized genomic vaccine to elicit a patient-specific anti-tumor response. METHODS: Normal and tumor DNA and tumor RNA are extracted from tumor specimens and PBMCs. Exome and RNA sequencing and HLA typing is performed for each patient. Neoantigens are identified using the OpenVax computational pipeline, which calls somatic variants in the DNA and prioritizes corresponding candidate neoantigens for vaccination based on tumor RNA expression and predicted MHC class I binding affinity for each of the patient's HLA alleles. This work is the base for a phase I trial of personalized neoantigen vaccines in combination with Tumor Treating Fields for GBM (NCT03223103). RESULTS: For each of the 9 patients enrolled in the trial, an average of 1005 somatic mutations were identified (range 299–2441), of which 118 were coding variants (range 52–198), 20 were coding and expressed in the tumor RNA (range 9–45), and 16 were coding, expressed and resulted in predicted MHC class I ligands (range 7–33). An average of 2.3% of all somatic variants identified in each tumor gave rise to predicted neoantigens. Sufficient numbers of neoantigens were identified in all tumor samples of the patients enrolled in the study. The overall somatic mutation landscape for the tumors revealed 4/9 PIK3R1 deletions, 2/9 IDH1 substitutions, as well as disruptions in PTEN, TP53, and ATRX, among others. CONCLUSIONS: Identifying sufficient neoantigens for inclusion in the personalized genomic vaccine is computationally feasible despite a typically low GBM mutational burden. Driver and passenger mutations can be identified through the same computational pipeline utilized for other tumor types.

EPCO-23. COMPARATIVE TRANSCRIPTOMICS TO IDENTIFY TARGETED THERAPY CANDIDATES IN HIGH GRADE GLIOMA

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Genomic characterization is often used for the identification of therapeutic targets in tumors. Recently, comparative transcriptomics has begun to be utilized for this purpose. In this pilot, we compare the transcriptome of a patient with recurrent high grade glioma (HGG) to our cohort to identify potential therapies. We reviewed transcriptomic profiles from patients who had resection of HGG at our institution over the past year as well as the UCSC cancer compendium. Briefly, tumor RNA was extracted from embedded tumor tissue sections with tumor cellularity higher than 20%. RNA libraries were sequenced to obtain approximately 65 million reads on an Illumina HiSeq 4000 System utilizing patterned flow cell technology. The RNA profile of a 24 male with Li-Fraumeni syndrome and recurrent HGG with leptomeningeal spread underwent comparative transcriptomics to identify targets. A Bayesian statistical framework for gene expression outlier detection was used. These comparisons allowed for the identification of genes and pathways that are significantly overexpressed. Our internal HGG cohort consisted of 44 adult patients and was evenly distributed among the 4 HGG Verhaak subtypes. Our patient of interest had druggable outlier expression in HDAC1, STAT1 and STAT2 in comparison to our internal cohort indicating vorinostat and ruxolitinib as potential therapies, respectively. We then compared our patient of interest to 12,747 patients in the cancer compendium and STAT2 expression was high but not an outlier. In comparison to 738 glioma samples, STAT1 and STAT2 were outliers but not HDAC1 again indicating ruxolitinib as a potential targeted therapy. The patient did not have outlier expression in notch transcriptional targets or immune checkpoint biomarkers when compared to all cohorts. In conclusion, comparative Transcriptomics can identify therapeutic targets in a patient with recurrent HGG even in small cohorts. In our pilot, we identified ruxolitinib as a potential candidate to treat leptomeningeal recurrence.

EPCO-24. COMPUTATIONAL APPROACH TO IDENTIFYING NEUROINFLAMMATION IN GLIOBLASTOMA MULTIFORME (GBM)

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INTRODUCTION: Glioblastoma multiforme (GBM) is an aggressive brain cancer with dismal prognosis, despite aggressive surgery, radiation and chemotherapy. Therapies directed to the immune system are an exciting prospect in oncology and require an understanding of the interaction between tumors and immune cells. Our objective was to use computational tools to estimate immune infiltration in GBM and determine whether specific immune cell types are associated with clinical outcomes. METHODS: RNA sequencing and targeted DNA sequencing (to 981 oncology genes) was performed from 37 surgically-resected GBM tumors. Tumor mutations were identified, and gene-level transcript counts were used to estimate tumor-associated cell types using bioinformatics tools. Clinical variables, including survival from surgery and diagnosis, were collected and tested for associations with molecular data. RESULTS: We detected leukocyte fractions (i.e., immune infiltration) ranging from 2% to 50% in GBMs, with an average of 10.2%. Specifically, we found a statistically significant association between high Th2 cell estimates and reduced overall survival (from both surgery and diagnosis). Nine patients with high Th2 tumors had a median OS from surgery of 187 days, compared with a median of 454 days for 28 patients with low Th2 tumors (log-rank Matel-Cox test; $p = 0.0023$, HR = 3.1). We also found an association between *NF1* mutant tumors, which were enriched for a KRAS signaling signature, and high immune infiltration ($p < 0.05$). CONCLUSION: Our computationally-driven approach predicted significant immune infiltration in GBM and a potential association between poor prognosis and Th2 cells. The specific class of CD4+ helper T-cells is generally associated with poor anti-tumor immunity and a Th2-bias has been reported in gliomas. Our data adds to the collective understanding of the molecular landscape of GBM, as well as the complex immune environment, which will have important implications in tumor treatment and prognosis.

EPCO-25. AN IMMUNOMETHYLOMIC PLATFORM INTEGRATING SYSTEMIC IMMUNE PROFILES AND EPIGENETIC AGE IN NEURO-ONCOLOGY

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Lineage-specific DNA methylation marks differentiate leukocyte cell types while individual biological aging mechanisms impact other methylation alterations. Human glioma incidence and survival times have been shown to be associated with aberrant immune profiles and have a strong dependency on age. Here we developed a single epigenetic analysis framework to evaluate both immune cell fractions and epigenetic age in peripheral blood. We examined these measures in archived blood from 197 triple-negative glioma patients (TNG; *IDH* wildtype, 1p19q intact and TERT wildtype) and 312 frequency-matched controls from the SF Bay Area Adult Glioma Study (AGS). Significant differences were observed with TNG cases having lower CD4 and CD8 T cell, natural killer, and B cell fractions, and higher neutrophil fractions than controls. TNG cases were significantly older than controls in two of three epigenetic age estimates; however, there was no difference in epigenetic age acceleration once immune cell proportions were considered. For the TNG cases, we augmented results from several machine learning methods to delineate risk groups of TNG patients with significantly different overall survival. We compared survival models built by recursive partitioning, random forest, and elastic net methods. The final model was chosen by repeated bootstrap sampling via the Brier score loss function and validated in an independent set of 72 *IDH*-mutant only or *TERT*-mutant only glioma patients also from the AGS. The final model indicated important interactions between immune cell fractions (including CD4 and CD8 T cells and neutrophils) and treatment, age, and dexamethasone status when adjusted for the main effects of epigenetic age, glioblastoma status, and the neutrophil-to-lymphocyte ratio. The capacity of immunomethylomics to capture diverse, clinically relevant information and the simplicity of its implementation make this a powerful tool for personalized patient evaluation in the neuro-oncology clinic.

EPCO-26. PROJECT HOPE: "PEDIATRIC AND AYA *HI*GH-GRADE GLIOMA *OMICS PROJE*CT"- A LONGITUDINAL MOLECULAR LANDSCAPE OF HIGH-GRADE GLIOMAS RESOLVED AT SINGLE-CELL LEVEL

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