Title

BIOM-13. DNA METHYLATION MARKS GLUCOCORTICOID PATHWAY RESPONSE IN DEXAMETHASONE-TREATED BRAIN TUMOR PATIENTS

Journal

Neuro-oncology, 22(Suppl 2)

ISSN

1522-8517

Authors

Wiencke, John
Molinaro, Annette
Warrier, Gayathri
et al.

Publication Date

2020-11-01

Peer reviewed

BIOM-12. CIRCULATING TUMOR DNA IN ADULTS WITH GLIOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF BIOMARKER SENSITIVITY

James McMahon[1], Matthew Studer[1], Bryan Ulrich[1], and Gustavo Pradilla[2]; [1]Emory University School of Medicine, Atlanta, GA, USA, [2]Department of Neurosurgery, Atlanta, GA, USA

BACKGROUND: Circulating tumor DNA (ctDNA) has emerged as a promising non-invasive biomarker to capture tumor genetics in patients with primary brain tumors. Research into its clinical utility, however, has not been standardized, as performance statistics of ctDNA remain undefined and optimal ctDNA assay and biospecimen sources for its evaluation have not been conclusively identified. We sought to determine a pooled sensitivity of the detection ctDNA in both CSF in plasma when compared to detecting the same mutant DNA in tumor tissue of gliomas. We then sought to compare ctDNA sensitivity between these two reservoirs, as well as between individual WHO grades of glioma. METHODS: Following PRISMA guidelines, systematic review and meta-analysis was performed using published studies that assessed circulating tumor DNA in either plasma or CSF among adult patients with histopathology-confirmed glioma. Weighting of individual studies was conducted to reach an overall pooled sensitivity of ctDNA detection in both CSF and plasma. Chi-squared tests of independence were performed to compare overall sensitivity of ctDNA in CSF versus plasma, as well as to estimate the sensitivity of ctDNA for each WHO grade of glioma. RESULTS: The overall reported sensitivity of ctDNA in CSF was found to be 77.4%, significantly higher than the 38.8% sensitivity in plasma ($p < 0.0001$). Sensitivity was significantly higher for high grade (82.8%) than low grade (60.5%) tumors in CSF ($p=0.0023$), and sensitivity was found to sequentially increase with increasing WHO grade. Qualitative analysis revealed evidence of greater sensitivity among single-allele PCR or small targeted next generation sequencing (NGS) panels, and increased sensitivity among larger tumors and those in proximity to cisternal or ventricular CSF. CONCLUSION: Circulating tumor DNA is potentially a highly sensitive non-invasive biomarker among adults with gliomas. To maximize its sensitivity, CSF should be studied with targeted genetic analysis platforms, particularly in suspected high-grade gliomas.

BIOM-13. DNA METHYLATION MARKS GLUCOCORTICOID PATHWAY RESPONSE IN DEXAMETHASONE-TREATED BRAIN TUMOR PATIENTS

John Wiencke[1], Annette Molinaro[1], Gayathri Warrier[1], Terri Rice[1], Jennifer Clarke[1], Jennie Taylor[1], Margaret Wrensch[1], Stanley Tamaki[1], JiYoon Lee[1], Helen Hansen[1], Lucie McCoy[1], Paige Bracci[2], Lucas Salas[3], Devin Koestler[4], Brock Christensen[3], and Karl Kelsey[5]; [1]Department of Neurological Surgery, University of California (UCSF), San Francisco, San Francisco, CA, USA, [2]Department of Epidemiology & Biostatistics, UCSF, San Francisco, CA, USA, [3]Department of Epidemiology, Dartmouth College, Lebanon NH, USA, [4]Department of Biostatistics & Data Science, University of Kansas Medical Center, Kansas City KS, USA, [5]Department of Epidemiology, Brown University, Providence, RI, USA

Dexamethasone (DEX) is routinely prescribed in brain tumor patients to limit vasogenic edema but may also exacerbate immunosuppression and adversely affect survival. The wide spectrum of dosing and individual variation in glucocorticoid (GC) response makes it difficult to assess the impact of DEX exposures. A potential marker of steroid pathway activation and GC load affecting the immune system are induced changes in chromatin structure marked by DNA methylation. We identified DEX-responsive DNA methylation sites in blood leukocytes from glioma patients treated with the drug at various doses and times during the course of their disease. Using weighted co-methylation network analysis, we show that DEX-induced hypomethylation includes well-known regulators of GC receptor (GR) sensitivity (e.g., FK506 binding protein 51: FKBP5) and inflammation (e.g., myeloperoxidase: MPO) and is enriched at genomic locations containing glucocorticoid receptor (GR) binding sites. Elastic net regression modeling was used to train a multilocus GC methylation index (GCMI) that discriminates current DEX users and non-users. GCMI scores showed wide interindividual variation among cases and DEX naïve control subjects. Using independent samples of DEX naïve and exposed glioma patients we show that the GCMI is a sensitive and specific indicator of DEX exposure. GCMI measured in non-glioma controls indicated sensitivity to non-DEX steroid treatments (e.g. prednisolone, fluticasone). Subjects with elevated neutrophil and decreased lymphocyte counts demonstrated high GCMI scores, reflecting the clinically relevant *in vivo* impact of this marker. Among 195 IDH wildtype and hTERT non-mutant glioma subjects, the GCMI was associated with a HR of 1.11 (95% CI 1.06–1.17) $p < 0.0001$ in Cox survival models that included age and tumor grade. We conclude that epigenetic remodeling in the peripheral immune compartment in response to DEX exposures is a rich source of potentially powerful markers of individual response to GC pathway activation and associated alterations in the immune response.

BIOM-14. METHODS FOR SCREENING AND MONITORING BY GBM MASTER REGULATORY GENE MARKERS IN LIQUID BIOPSY

Tianyi Liu, Son Le, and David Tran; University of Florida, Gainesville, FL, USA

BACKGROUND: Current liquid-based cancer screening relies on massive deep NGS to detect rare cancer cell-derived genetic materials - a costly method fraught with high false-negative and false-positive rates. We aim to develop a non-NGS-centered, AI-directed liquid-based detection of GBM stem-like cells (GSC). METHODS: Utilized a robust AI suite, NETZEN, we defined a common master regulatory gene network (MRGN) in GSC. Since master regulators (MR) in MRGN are developmentally restricted, their chromosomal loci are accessible in GSC but not in normal cells. Downstream factors in MRGN are massively overexpressed in GSC compared to normal cells. Thus, we measured 1) accessibility of MR genes using transposase/transposons carrying unique barcodes that can be detected after insertion into the MR's predetermined accessible locations, and 2) expression of downstream factors using nested qRT-PCR, in PBMC from healthy controls spiked with known quantities of GSC or patients with GBM. RESULTS: We characterized 10 MR genes in GSC with ≥1 GC-rich promoter region that is hypomethylated and accessible (ATACseq) in GBM/GSC per GSE70175/92460/52271 (19 samples) and GSE67633/96088 (14 samples), and hypermethylated and inaccessible in lymphocytes/PBMC per GSE98837 (6) and GSE74912 (13), respectively. Using barcoded transposons, we specifically disrupted 4 MR's accessible regions only in GSC, not in PBMC. We also characterized 50 upregulated downstream factors with the top 20 having 3 to 5-orders-of-magnitude higher mean expression in GSC compared to PBMC (GSE79362/86884, 451 samples). Currently our method has a detection limit of 0.2–1 GSC in 10^6 PBMC. Using the first iteration, we detected GSC's MRGN in blood samples of 14/14 GBM patients before resection, compared to in none of 15 healthy donors. CONCLUSIONS: Chromosomal accessibility of MR and signal amplification in MRGN of GSC provide powerful substrates for a non-NGS, low-cost, liquid-based GBM detection system with potentially high sensitivity and specificity. Further testing and optimization are ongoing.

BIOM-15. SUBVENTRICULAR ZONE INVOLVEMENT IS ASSOCIATED WITH WORSE OUTCOME IN GLIOMA WHO GRADE II INDEPENDENT OF MOLECULAR MARKERS

Philipp Karschnia[1], Jonathan Weller[2], Jens Blobner[1], Veit M. Stoecklein[1], Mario M. Dorostkar[3], Kai D. Rejeski[4], Robert Forbrig[5], Maximilian Niyazi[6], Louisa von Baumgarten[7], Jorg Dietrich[8], Joerg-Christian Tonn[1], and Niklas Thon[1]; [1]Department of Neurosurgery, Ludwig-Maximilians-University School of Medicine, Munich, Germany, [2]Department of Neurosurgery, Ludwig-Maximilians-University School of Medicine, München, Germany, [3]Center for Neuropathology and Prion Research, Ludwig-Maximilians-University School of Medicine, Munich, Germany, [4]Department of Medicine III, Ludwig-Maximilians-University School of Medicine, Munich, Germany, [5]Department of Neuroradiology, Ludwig-Maximilians-University School of Medicine, Munich, Germany, [6]Department of Radiation Oncology, Ludwig-Maximilians-University School of Medicine, Munich, Germany, [7]Department of Neurosurgery, Ludwig-Maximilians-University School of Medicine, Munich, Bayern, Germany, [8]Department of Neurology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

BACKGROUND: The subventricular zone represents a niche of adult neural stem cells. Involvement of the subventricular zone is associated with decreased survival in malignant glioma. We aimed to determine whether a similar association applies to low-grade gliomas. METHODS: A retrospective institutional database search was performed for patients with glioma WHO grade II according to the 2016 classification. Demographic data, histology and molecular signature, imaging, and therapy were recorded and outcome was analysed for tumors with and without infiltration of the subventricular zone. RESULTS: 182 patients with glioma WHO grade II were identified, including 97 oligodendrogliomas and 85 astrocytomas. 78 of 182 patients (43%) presented with subventricular zone involvement. Demographics, histopathology, and molecular signature did not differ between patients with and without subventricular zone involvement. First-line management included surgery, chemotherapy, radiotherapy, brachytherapy, and wait-and-scan approaches. Median follow-up was 43 months. Median time to malignant progression was 122 months; median overall survival was not reached. Subventricular zone involvement was a negative prognostic marker for time to malignant progression ($p = 0.002$) and overall survival ($p = 0.023$) in the entire cohort as well as in the subgroup of patients who were managed with wait-and-scan approaches. Among patients in which early therapy was provided, subventricular zone involvement was not prognostic for overall survival but for time to malignant progression. In multivariate analysis, subventricular zone involvement was associated with worse prognosis independent of molecular markers or treatment approaches including use of resection. CONCLUSION: Subventricular zone involve-