Title

BIOM-43. CROSS-PLATFORM ROBUSTNESS IN THE GLUCOCORTICOID RESPONSE PHARMACODYNAMIC BIOMARKER

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cations for postoperative radiotherapy are controversial. DNA methylation profiling, copy number variants (CNVs), exome sequencing, and RNA sequencing have improved understanding of meningioma biology, but have not superseded histologic grading, or revealed biomarkers for radiotherapy responses. To address these unmet needs, we optimized and validated a targeted gene expression biomarker predicting meningioma outcomes and responses to radiotherapy. METHODS: Targeted gene expression profiling was performed on a discovery cohort of 173 meningiomas (median follow-up 8.1 years) and a validation cohort of 331 meningiomas (median follow-up 6.1 years) treated with surgery (n=504) and postoperative radiotherapy (n=73) at independent, international institutions (70% WHO grade 1, 24% WHO grade 2, 6% WHO grade 3). Optimized targeted gene expression models predicting clinical outcomes (34 genes) or radiotherapy responses (12 genes) were developed from the discovery cohort, and compared to histologic and molecular classification systems by performing DNA methylation profiling, CNV analysis, exome sequencing, and RNA sequencing on the same meningiomas. RESULTS: Targeted gene expression profiling achieved a concordance-index of 0.75 ± 0.03 (SEM) for local freedom from recurrence (LFFR) and 0.72 ± 0.03 for overall survival (OS) in the validation cohort, outperforming WHO grade (5-year LFFR delta-AUC 0.15, 95% CI 0.076-0.229, p=0.001) and DNA methylation grouping (delta-AUC 0.075, 95% CI 0.006-0.130, p=0.01) for LFFR, disease-specific survival, and OS. The biomarker was independently prognostic after accounting for WHO grade, extent of resection, primary versus recurrent presentation, CNV status, DNA methylation group, and Ki67 labeling index, and identified meningiomas benefiting from radiotherapy (interaction p-value=0.0008), suggesting postoperative radiotherapy could be refined in 30.2% of cases. CONCLUSIONS: Targeted gene expression profiling of 504 meningiomas improves discrimination of meningioma local recurrence, disease-specific survival, and overall survival, and predicts radiotherapy responses.

BIOM-41. LIVE-CELL IMAGING SHOWS UNEVEN SEGREGATION OF EXTRACHROMOSOMAL DNA ELEMENTS AND TRANSCRIPTIONALLY ACTIVE EXTRACHROMOSOMAL DNA CLUSTERS IN CANCER

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Oncogenic extrachromosomal DNA elements (ecDNAs) promote intratumoral heterogeneity, creating a barrier for successful cancer treatments. The underlying mechanisms are poorly understood and studies are hampered in part by a lack of adequate tools enabling studies of ecDNA behavior. Here, we show that single-cell ecDNA copy numbers greatly vary between tumor cells, both in vitro and in patient glioblastoma specimens, suggesting uneven ecDNA segregation during mitosis. We established a CRISPR-based approach which leverages unique ecDNA breakpoint sequences to tag ecDNA with fluorescent markers in living cells. Applying this method during mitosis revealed disjointed ecDNA inheritance patterns, providing an explanation for rapid ecDNA accumulation in cancer. Post-mitosis, ecDNAs tended to cluster and clustered ecDNAs colocalized with RNA polymerase II, promoting transcription of cargo oncogenes. Our observations provide direct evidence for uneven segregation of ecDNA and sheds new light on mechanisms through which ecDNAs contribute to oncogenesis.

BIOM-42. IMMUNOHISTOCHEMICAL ASSESSMENT OF MEMBRANOUS SOMATOSTATIN TYPE 2A RECEPTOR (SST2A) EXPRESSION ACROSS HIGH-RISK PEDIATRIC CENTRAL NERVOUS SYSTEM (CNS) TUMORS

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INTRODUCTION: ^{77}Lu-DOTATATE, a radionuclide therapy which binds SST2A, has demonstrated efficacy in neuroendocrine tumors and evidence of CNS penetration, supporting potential expansion within pediatric neuro-oncology. Understanding the prevalence of SST2A expression across pediatric CNS tumors is essential to identify patients who may benefit from somatostatin receptor-targeted therapy and to further elucidate the oncogenic role of SST2A. METHODS: SST2A immunohistochemistry (IHC) was performed on tumor specimens and interpreted by two experienced pathologists (blinded), utilizing semi-quantitative scoring of membranous expression within viable tumor. Immunoreactive cell percentage was visually scored as 0 (none), 1 (< 10%), 2 (10-50%), 3 (51-80%), or 4 (>80%). Staining intensity was scored as 0 (none), 1 (weak), 2 (moderate), or 3 (strong). Combined scores for each specimen were calculated by multiplying percent immunoreactivity and staining intensity values (range=0-12). RESULTS: A total of 117 tumor samples from 113 patients were analyzed. Significant differences in SST2A IHC scores were observed across histopathologic diagnoses, with consistently high scores in medulloblastoma (mean±SD=7.6±3.6 [n=36]) and meningioma (5.7±3.4 [n=15]), compared to minimal or absent expression in ATRT (0.3±0.6 [n=3]), ETMR (1.0±0 [n=3]), ependymoma (grades I-III; 0.2±0.7 [n=26]), and high-grade glioma (grades III-IV; 0.4±0.7 [n=22]). Pineoblastoma (3.8±1.5 [n=4]) and other embryonal tumors (2.3±3.8 [n=8]) exhibited intermediate, variable expression. Among expressors, there was no association between SST2A IHC score and patient age, sex, presence of metastases, likelihood of relapse, or prior treatment. In a subset of paired primary and recurrent specimens from 3 patients, SST2A IHC scores remained largely unchanged. Among medulloblastomas, SST2A IHC scores were higher in non-SHH (8.6±3.2) than SHH (5.0±3.3) molecular subgroups (p=0.033). CONCLUSIONS: High membranous SST2A expression was demonstrated in medulloblastoma, meningioma, and some rarer embryonal tumors with potential diagnostic, biologic, and therapeutic implications. Somatostatin receptor-targeted therapy such as ^{177}Lu-DOTATATE deserves further investigation in these highly SST2A-expressing pediatric CNS tumors.

BIOM-43. CROSS-PLATFORM ROBUSTNESS IN THE GLUCOCORTICOID RESPONSE PHARMACODYNAMIC BIOMARKER

Emily Tang[1], John Wiencke[1], Gayathri Warrier[1], Helen Hansen[1], Lucie McCoy[1], Terri Rice[1], Paige Bracci[1], Margaret Wrensch[1], Jennie Taylor[2], Jennifer Clarke[1], Devin Koestler[3], Lucas Salas[4], Brock Christensen[4], Karl Kelsey[5], and Annette Molinaro[1]; [1]University of California San Francisco, San Francisco, CA, USA, [2]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, [3]University of Kansas Cancer Center, Kansas City, KS, USA, [4]The Geisel School of Medicine at Dartmouth, Hanover, NH, USA, [5]Brown University, Providence, RI, USA

The neutrophil dexamethasone methylation index (NDMI) is an algorithm-based biomarker to assess individuals' exposures to dexamethasone, a synthetic glucocorticoid commonly administered for inflammation. Cortisol is the main endogenous glucocorticoid that controls vital processes including the immune response and lipid and carbohydrate metabolism. Variations in the NDMI score reflect individuals' sensitivities of exposures to both exogenous and endogenous glucocorticoids, and this biomarker was trained using elastic net regression on Illumina's most recent DNA methylation beadarray, the EPIC array, which contains 850,000 cytosine-guanine (CpG) sites. While technology for microarray research continues to advance over time, researchers are capable of conducting more comprehensive epigenome-wide association studies (EWAS). However, many studies are still run and archived using Illumina's historical 450K platform with approximately 450,000 CpGs, and there are fewer published databases using the 850K EPIC array. To evaluate the cross-platform bioinformatic comparability, we performed elastic net regression modeling using predictors available in the 450K to train the NDMI. Among the 135 pre-surgery glioma cases from the UCSF Immune Profiles Study (IPS), NDMI scores between the 450K and 850K model were strongly correlated ($r = 0.99$, $p < 0.0001$). In the 311 controls from the UCSF Adult Glioma Study (AGS), similar correlations were observed ($r = 0.96$, $p < 0.0001$). We observe that NDMI remains a robust tool using historical 450K data and conclude that this algorithmic tool is capable of detecting the variations in individuals' responses to dexamethasone.

BIOM-44. PRE-SURGICAL ADVANCED MRI IS USEFUL FOR FORECASTING DRUG DISTRIBUTION IN BRAIN TUMORS

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Choosing effective chemotherapies for intravenous delivery to brain tumors is challenging, especially given the protective nature of the blood brain barrier (BBB). Connecting drug distribution to non-invasive, pre-surgical magnetic resonance imaging (MRI) could allow for predictive insight into drug distribution. In a previous study, we found that T2Gd images were pre-