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ABSTRACTS

ABSTRACTS FROM: BASIC AND TRANSLATIONAL OMICS OF BRAIN TUMORS AND THEIR MICROENVIRONMENT

Submission Categories and Abbreviations:
CSAO – Computational and Statistical Approaches for Omics
ECOA – (Epi)genetics and Computational Omics in Adults
MOMC – Multi-omics
NGMA – Next-Generation Methods and Approaches
OPTC – Omics in Molecular Pathology & Tumor Classification
OMRT – Omics of Response to Therapy
OTEH – Omics of Tumor Evolution and Heterogeneity
OTME – Omics of the Tumor Microenvironment

FINAL CATEGORY: COMPUTATIONAL AND STATISTICAL APPROACHES FOR OMICS

CSAO-1. INTERROGATIVE BIOLOGY: UNRAVELING INSIGHTS INTO CAUSAL DISEASE DRIVERS BY USE OF A DYNAMIC SYSTEMS BIOLOGY AND BAYESIAN AI TO IDENTIFY THE INTERSECT OF DISEASE AND HEALTHY SIGNATURES

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The past decade has been witness to an explosive proliferation of data analytics modalities, all seeking to unravel insight into large-scale data sets. Machine learning and AI methodologies now occupy a central role in analyses of data sets that range in nature from genomics, "omics", clinical, real-world evidence, and demographic data. Despite advances in data analytics/machine learning, access to complex population level clinical and related datasets, translating information into actionable guidance in human health and disease remains a challenge. Interrogative Biology, a systems biology/AI platform generates an unbiased, data-informed network for identifying targets (disease drivers) and biomarkers for disease interception at the point of transition to dysregulation, preceding clinical phenotype. The data topology is enabled by a systematic acquisition and interrogation of longitudinal bio-samples of clinically annotated human matrices (e.g. blood, urine, saliva, tissues) subjected to comprehensive multi-omic (genomic, proteomics, lipidomics and metabolomics) profiling over time. The molecular profiles are integrated with clinical health information using Bayesian artificial intelligence analytics, bAIcis, to generate causal network maps of overall health. Differentials between "health" and "disease" network maps identifies drivers (targets and biomarkers) of disease and are rapidly validated in orthogonal wet-lab disease specific perturbed model systems. Target information imputed into the bAIcis framework can define therapeutic strategies including identification of existing drugs and bio-actives for corrective response. Using a combination of clinic based sampling and dried blood spot analysis for longitudinal dynamic monitoring of markers of health-disease status provides opportunity for proactive clinical management and intervention for corrective response in advance of major deterioration of health status. Taken together, the approach herein allows for health surveillance based on in-depth biological profiling of alterations in the patient narrative to guide treatment modalities and strategies in a longitudinal and dynamic manner to identify, track, intercept, and arrest human disease.

FINAL CATEGORY: (EPI)GENETICS AND COMPUTATIONAL OMICS IN ADULTS

ECOA-2. IMMUNO-SENSITIZATION OF GLIOBLASTOMA TO NY-ESO-1 TARGETING VIA PROMOTER DEMETHYLATION

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INTRODUCTION: The immunotherapeutic targeting of New York-esophageal squamous cell carcinoma (NY-ESO-1) and other cancer/testis antigens (CTA) is an appealing strategy for the treatment of malignant gliomas because CTA are not expressed in most normal adult tissues and their expression can be induced in tumors for targeting by T-cells. Basally, NY-ESO-1 is often poorly expressed in glioblastoma (GBM), presumably through promoter methylation. Mechanisms governing the expression of CTA have been explored in other cancers; however, neither the prevalence of NY-ESO-1 downregulation in GBM patient tumors nor the presumed mechanism of downregulation by promoter methylation in GBM has been formally established. METHODS: We characterized baseline CpG methylation of NY-ESO-1 in 30 bulk patient GBM samples, 10 patient-derived gliomaspheres, and three established tumor cell lines using bisulfite sequencing. We induced NY-ESO-1 expression *in vitro* in U251 human GBM cells using the hypomethylating agent decitabine (DAC). We investigated the epigenetic response of DAC-treated U251 with bisulfite sequencing and NY-ESO-1 expression with quantitative real-time PCR. Lastly, we performed single-cell RNA sequencing on DAC-treated GBM U251 to evaluate tumor subpopulations that upregulate NY-ESO-1 and other co-expressed CTA after DAC treatment. RESULTS: Baseline NY-ESO-1 expression is associated with promoter methylation in the majority of GBM. Treatment of cells with 1 μM DAC every day for 4 days explicitly demethylated the promoter region of NY-ESO-1 and resulted in a 1000-fold increase in mRNA expression. DAC treatment upregulates NY-ESO-1 coordinately with other cancer/testis antigens CTAG2 and MAGEA4 as demonstrated by single-cell RNA sequencing. CONCLUSION: Exposure of U251 to DAC results in promoter demethylation in NY-ESO-1 and increased expression of CTA. DAC treatment may therefore render GBM susceptible to targeting of these antigens by T-cells, revealing a feasible strategy of NY-ESO-1 and co-expressed CTA promoter demethylation to sensitize GBM to immunotherapy.

ECOA-3. MLL4, UTX, AND EZH2 REGULATE THE EXPRESSION OF TRANSCRIPTION FACTORS ASSOCIATED WITH THE EPITHELIAL-TO-MESENCHYMAL TRANSITION OF LUNG CANCER DURING METASTASIS TO THE BRAIN AT POSTTRANSCRIPTIONAL STEPS

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PURPOSE. The objective of this study was to investigate the epigenetic role of histone lysine methylation/demethylation on the expression of epithelial-to-mesenchymal transition (EMT) associated transcriptional factors (TFs) during the metastasis of lung adenocarcinoma to the brain. METHODS. Paired samples of lung adenocarcinoma and brain metastasis (BM) were analyzed in 46 individual patients. Both samples were obtained by surgical resection or biopsy of the lung and brain. The paraffin-fixed formalin-embedded samples were obtained from the pathology archives in our institute. In samples of lung adenocarcinoma and BM, immunohistochemical staining was performed for epithelial markers, mesenchymal markers, EMT-TFs, histone lysine methyltransferase and demethylase. And the verification of the present result was performed by qRT-PCR. RESULTS. The immunoreactivity of EMT-TFs such as Slug (15.6% vs. 42.6%, p = 0.005), Twist (23.6% vs. 45.9%, p = 0.010) and ZEB1 (15.0% vs. 55.9%, p = 0.002) was increased in BM compared with that in lung adenocarcinoma. Epigenetic inducers such as H3K4 methyltransferase (MLL4, p = 0.018) and H3K36me3 demethylase (UTX, p = 0.003) were statistically increased, and epigenetic repressors such as EZH2 (H3K27 methyltransferase, p = 0.046) were significantly decreased in BM compared with those in lung adenocarcinoma. The expression of UTX-ZEB1 (R2 linear = 1.204) and MLL4-Slug (R2 linear = 0.987) was increased in direct proportion, and EZH2-Twist (R2 linear = - 2.723) decreased in reverse proportion. The qRT-PCR showed the same results. CONCLUSION. The results suggest that certain histone lysine methyltransferase/demethylase, such as MLL4, UTX, and EZH2, regulate the expression of EMT-TFs such as Slug, ZEB1, and Twist epigenetically, which may thereby influence cancer metastasis from the lung to the brain.

ECOA-4. HYPOXIA ALTERS THE DNA METHYLATION PROFILE OF GLIOBLASTOMA TUMOR CELLS

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Glioblastoma (GBM) is the deadliest and most vascularized brain tumor in adults; however, blood circulation is highly inefficient in these tumors, contributing to areas of cell death (necrosis) within the tumor, which is likely due to oxygen deprivation (hypoxia). Hypoxia plays a major role in tumor growth, invasion, and resistance to therapy. Hypoxic stress has been linked to several changes that are fundamental to the malignant progression of GBM and other tumor types. Pimonidazole (PIMO) is an exogenous marker of hypoxia that is used to delineate hypoxic regions in