Absocts

MOMC-3. HYPERMETHYLATION AND OVEREXPRESSSION OF HOX GENES ARE POOR PROGNOSTICATORS IN LOWER-GRADE GLIOMA
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Diffuse gliomas represent over 80% of malignant brain tumors ranging from low-grade to aggressive high-grade lesions. Molecular characterization of these tumors led to the development of new classification system comprising specific glioma subtypes. While this provides novel molecular insight into gliomas it does not fully explain the variability in patient outcome. To identify and characterize a predictive signature of outcome in diffuse gliomas, we utilized an integrative molecular analysis (methylation, mRNA, copy number variation (CNV) and mutation data) using multiple molecular platforms, including a total of 310 IDH mutant glioma samples from University Health Network (UHN) and German Cancer Research Center (DKFZ) together with 419 samples from The Cancer Genome Atlas (TCGA). Cox regression analysis of methylation data from the UHN cohort identified CpG-based signatures that split the glioma cohort into two prognostic groups strongly predicting survival (p-value < 0.0001). The CpG-based signatures were reliably validated using two independent datasets from TCGA and DKFZ cohorts (both p-values < 0.0001). The results show that the methylation signatures that predict poor outcome also correlated with G-CIMP low status, elevated CNV instability and hypermethylation of a set of HOX gene probes. Further study in diffuse lower-grade glioma (LGG) using integrated mRNA and methylation (iRM) analyses showed that parallel HOX gene overexpression and hypermethylation in the same direction were significantly associated with increased mutational load, high aneuploidy and worse survival (p-value < 0.0001). Furthermore, this iRM high group was characterized by a 7-HOX gene signature showed significant survival differences not only in IDH mutant LGG but also in IDH wildtype LGG. These results demonstrate the importance of HOX genes in predicting the outcome of diffuse gliomas to identify relevant molecular subtyping independent of histology.

MOMC-4. PROTEOGENOMIC AND METABOLOMIC CHARACTERIZATION OF Glioblastoma
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Glioblastoma (GBM) is the most aggressive systemic cancer, with median survival under 2 years. Understanding its molecular pathogenesis is crucial for improving diagnosis and treatment. We performed an integrated analysis of genomic, proteomic, post-translational modification and metabolomic data on 99 treatment-naive GBMs. We identified key phosphorylation events (e.g., phosphorylated PTPN11 and PLCG1) as potential switches mediating oncogenic pathway activation as well as potential targets for EGFR-, TP53- and RB1-altered tumors. We detected immune subtypes, driven by the presence of immune cell populations using ddPCR, validated by single nucleic RNA sequencing (snRNA-seq), and they were correlated with specific expression and histone acetylation patterns. Acetylation of histone H2B in classical-like and immune-low GBM was driven largely by BRD4, CREBBP, and EP300. Integrated metabolic and proteomic data identified specific lipid distributions across subtypes and distinct global metabolic changes in IDH mutated tumors. This work highlights biological relationships which could potentially aid GBM patient stratifications for more effective treatments.

MOMC-5. SYSTEMS PHARMACOGENOMICS IDENTIFIES NOVEL TARGETS AND CLINICALLY ACTIONABLE THERAPEUTICS FOR MEDULLOBLASTOMA
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BACKGROUND: Medulloblastoma (MB) is the most common malignant pediatric brain tumor and a leading cause of cancer-related mortality and morbidity. Existing treatment protocols are aggressive in nature resulting in significant neurological, intellectual and physical disabilities for the children treated for this disease. Clearly, there is an urgent need to develop new and effective therapies that minimize these harmful side effects. METHODS: We identified candidate drugs for MB using a network-based systems-pharmacogenomics approach: based on results from a functional genomics screen, we identified a network of interactions implicated in human MB growth regulation. We then integrated drugs and their known mechanisms of action, along with gene expression data from a large collection of medulloblastoma patients to identify drugs with potential to treat MB. RESULTS: Our analyses identified drugs targeting CDK4, CDK6, and AURKA as strong candidates for MB, all of these genes are well validated as drug targets in other tumour types. We also identified non-WNT MB as a novel indication for drugs targeting TUBB, CAD, SNRPA, SLCA13, PTPR, P4HB and CHECK. Based upon these analyses we subsequently demonstrated that one of these drugs, the new multitargeted agent, oxabepine, blocked tumour growth in vivo in mice bearing Sonic Hedgehog and Group 3 patient-derived xenografts, providing the first demonstration of its efficacy in MB. CONCLUSIONS: Our findings confirm that this data-driven systems pharmacogenomics strategy is a powerful approach for the identification and validation of novel therapeutic candidates relevant to MB treatment, and along with data validating oxabepine in PDX models of the most aggressive subtypes of medulloblastoma, we present the network analysis framework as a resource for the field.

FINAL CATEGORY: NEXT GENERATION METHODS AND APPROACHES
NGMA-1. QUANTIFICATION OF IDH MUTANT ALLELES PREDICTS OUTCOME IN DIFFUSE GliOMA
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BACKGROUND: IDH mutation is the main factor used in the prognostication of diffuse gliomas, however within IDH mutated gliomas there still remains a high variability in both tumor progression and overall survival.1 Digital droplet polymerase chain reaction (ddPCR) is one of the latest molecular amplification techniques that offers high precision in addition to the ability of absolute quantification of mutant allele copies.2 METHODS: A total of 102 IDH mutant diffuse glioma tumor samples ranging from WHO grade 2 to 4 were collected. This cohort includes a total of 45 paired samples collected at two distinct surgical timepoints: initial and recurrent. All samples underwent DNA extraction. A total of 3 ng of tumor DNA from each sample was analyzed using ddPCR for the detection and quantification of IDH1 R132H mutant alleles. Sanger sequencing was performed on all samples with a high number of IDH mutant copies split by median demonstrated decreased overall survival (p = 0.04) and shorter progression free survival (p = 0.024). The number of IDH mutant copies was independent of WHO grade (p = 0.6) and 1p19q codeletion status (p = 0.86). Tumor pairs that had IDH mutant copies increase at recurrence were trending but not significantly related to a decrease in remaining survival (p = 0.1). CONCLUSIONS: ddPCR is a highly sensitive and specific method of detecting IDH mutations in diffuse gliomas. The number of IDH mutant copies in tumors at initial surgery can serve as an independent prognostic factor to help guide future treatment and follow-up.

NGMA-2. DUAL SGRNA-DIRECTED PD-L1 KNOCKOUT IN HUMAN GliOBLASTOMA CELLS USING THE CRISPR/CAS9 SYSTEM
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Glioblastoma multiforme (GBM) is an astrocyte derived brain tumor. It induces an immunosuppressive microenvironment by exploiting immune checkpoints such as the PD-1/PD-L1 pathway. Targeting the PD-1/PD-L1 pathway for immunotherapy is a promising new avenue for treating GBM, but more work is needed to develop a safe and effective method for clinical applications. We identified two sgRNA sequences located on PD-L1 exon 3. The first sgRNA recognized the forward strand of human PD-L1 and the second sgRNA recognized the reverse strand of exon 3 and cuts at a pair