endocrinopathy after treatment for medulloblastoma that can be used for future comparisons.

MEDULLOBLASTOMA (RESEARCH)

MBRS-01. DISSECTING REGULATORS OF THE ABERRANT POST-TRANSCRIPTIONAL LANDSCAPE IN MYC-AMPLIFIED GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common solid malignant pediatric brain neoplasm, with Group 3 (G3) MB representing the most aggressive subgroup. *MYC* amplification is an independent poor prognostic factor in G3 MB, however, therapeutic targeting of the MYC pathway remains limited and alternative therapies for G3 MB are urgently needed. Here we show that an RNA-binding protein, Musashi-1 (MSI1) is an essential mediator of G3 MB in both *MYC*-overexpressing mouse models and patient-derived xenografts. Unbiased integrative multi-omics analysis of MSI1 function in human G3 MB suggests a paradigm shift beyond traditional gene-based profiling of oncogenes. Here we identify MSI1 as an oncogene in G3 MB driving stem cell self-renewal through stabilization of HIPK1 mRNA, a downstream context-specific therapeutic target for drug discovery.

MBRS-02. BET BROMODOMAIN PROTEIN-KINASE INHIBITOR COMBINATIONS FOR THE TREATMENT OF MEDULLOBLASTOMA

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Recent sequencing studies have implicated many epigenetic regulators in medulloblastoma. The epigenetic reader protein Brd4 has been implicated in various cancers including medulloblastoma. Brd4 controls expression of the medulloblastoma essential genes *MYC* in G3 medulloblastomas, which have poor prognosis as well as *GLI1* and *GLI2* levels in Sonic hedgehog (SHH) driven medulloblastomas, which have intermediate prognosis. Highly selective Brd4 inhibitors have been developed that reduce *MYC*, *GLI1* and *GLI2* levels. These inhibitors have gone into clinical trials for multiple cancer indications including medulloblastoma. However, resistance is common for Brd4 inhibitors warranting combination therapies for improved clinical outcome. We have developed a computational pipeline termed SynergySeq that predicts patient specific combinations of Brd4 inhibitors along with kinase inhibitors. We demonstrate that Brd4-kinase inhibitors robustly reduce proliferation of Shh and MYC driven medulloblastoma cells. Improved efficacy is related to dampening the adaptive kinome reprogramming response that occurs after Brd4 inhibition. Our findings suggest that SynergySeq can be utilized to inform patient selection for clinical trials utilizing Brd4 inhibitors in medulloblastoma and other brain tumors.

MBRS-03. SINGLE NUCLEUS TRANSCRIPTOME PROFILES FROM HUMAN DEVELOPING CEREBELLUM REVEAL POTENTIAL CELLULAR ORIGINS OF MEDULLOBLASTOMA BRAIN TUMORS

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Medulloblastoma (MB) is a highly malignant pediatric brain tumor originating from the cerebellum and brainstem. Identification of molecular subgroups forming this heterogeneous tumor entity was initially achieved from transcriptome characterization and further strengthened using DNA methylation profiling. While subgroup classification improved clinical diagnosis and treatment options, the lack of knowledge of the cell-of-origin for some of the subgroups hinders further treatment improvements. In addition identification of the precise cells of origin for each subgroup could help to understand tumor cell biology. Single cell sequencing is the optimal way to solve this task; recently, there were attempts to uncover putative MB cell-of-origin by using such information obtained from mouse embryonic cerebellum. However, such a comparative strategy can miss important results due to the differences between mouse and human. To solve this issue, we performed global single nucleus sequencing on human cerebellum pre- and postnatal materials across several developmental time points and generated transcriptome profiles from ~200k single cells. We identified known cell types forming the human cerebellum and performed detailed comparison of normal cells to RNA-seq bulk data from MB brain tumors across all subgroups. By selecting an optimal analysis strategy, we verified granule neuron precursors as cells of origin for the SHH MB subgroup. Additionally, we also found other cell types in conjunction with the remaining MB subgroups, suggesting new potential targets for investigation. Notably, this strategy can be further applied to the examination of other brain tumors and has perspectives in medical application.

MBRS-04. MEDULLOBLASTOMA DETECTION BY BLOOD TEST

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INTRODUCTION: Long non coding RNAs (lincRNAs) are functionally defined as transcripts longer than 200 nucleotides in length with no protein coding potential. lincRNA involvement in human cancers etiology is being increasingly proved. Cancer-secreted long non-coding RNAs (lncRNAs) in exosomes are emerging mediators of cancer-host cross talk communication in tumor microenvironments. The ability to monitor and detect tumor markers in real time enables access to tumor biology and may allow highly personalized treatment for each patient. METHODS AND RESULTS: We analyzed RNA sequencing of 64 Medulloblastoma samples and quantified the genome wide long non coding RNAs (lincRNA) expression levels. We identified a lincRNA that is distinctively highly expressed in group 4 (MB4). MB4 expression was further examined in microarray analysis on a larger cohort of medulloblastoma patient samples and a large cohort (n=1405) of patient samples that include normal brain and different brain tumor samples. MB4 proved to be specific and highly expressed in group 4 Medulloblastoma. MB4 was detected in the plasma of medulloblastoma patients with active disease, or subtotal resection. MB4 was not detected in patients that their tumors were resected. MB4 expression is not detected in the serum of medulloblastoma type SHH, penioblastoma, ewing sarcoma and neuroblastoma patients. CONCLUSIONS: We have found that MB4 lncRNA is a highly specific medulloblastoma tumor biomarker and is sensitive and noninvasive biomarker that can be quantified from a blood test. MB4 can be a good diagnostic marker, and in future both may also be a good target for therapy.

MBRS-06. GLI3 INDUCES NEURONAL DIFFERENTIATION IN WNT- AND SHH- ACTIVATED MEDULLOBLASTOMA

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BACKGROUND: We have previously investigated the expression of Gli3, a downstream target of the Sonic Hedgehog pathway, which main function is to suppress Gli1/2 in medulloblastomas. We found that Gli3 is associated with neuronal and glial differentiation in desmoplastic / nodular (D/N) type medulloblastomas (Miyahara *et al.*, Neuropathology, 2013). In the present study, we investigated the expression of Gli3 in molecular subgroups. METHOD: Thirty-one medulloblastomas treated at Niigata University between 1982 and 2013 were studied. Molecular classification into 4 subgroups (WNT-activated, SHH-activated, Group 3 and Group 4) using Nanostring and immunohistochemistry was performed. Furthermore, Gli3 and Gli1 expression in molecular subgroups was assessed using public data bases. RESULTS: Nanostring was considered reliable (confidence > 0.9) in 28 cases. Four cases were classified as WNT-, 5 cases as SHH-activated, 4 cases as Group 3 and 16 cases as Group 4. Gli3 was positive in 7 out of 9 (78%) WNT-/SHH- cases, but positive in only 8 out of 19 (42.1%) non-WNT-/SHH- subgroup cases ($p = 0.1145$, Fisher's exact test). R2 database analysis confirmed that Gli3 was significantly elevated in WNT- and SHH-activated medulloblastoma. Gli1 was elevated in SHH-activated cases but suppressed in WNT-activated cases. IHC analysis revealed that Gli3 was elevated inside nodules showing neuronal differentiation in D/N type