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

MEDULLOBLASTOMA (RESEARCH)

MBRS-01. DISSECTING REGULATORS OF THE ABERANT 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 (MSH1) is an essential mediator of G3 MB in both MYC-overexpressing mouse models and patient-derived xenografts. Unbiased integrative multi-omics analysis of MSH1 function in humans G3 MB suggests a paradigm shift beyond traditional gene-based profiling of oncogenes. Here we identify MSH1 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 BROMODEDOM DOMAIN PROTEIN-KINASE INHIBITOR COMBINATIONS FOR THE TREATMENT OF MEDULLOBLASTOMA
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Recent sequencing studies have implicated many epigenetic regulators in 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 identifies 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 kinase 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 granule neuron precursors as cells of origin for the SHH MB subgroup. Additional identification of the precursors of cells 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 human cerebellum. However, such a comparative strategy can miss important results due to the differences between mouse and human. To solve this issue, we identified the transcriptional landscape 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 (lncRNAs) are functionally defined as transcripts longer than 200 nucleotides in length with no protein coding potential. lncRNA involvement in human cancers etiology is being increasingly proved. Cancer-secreted long non-coding RNAs (lncRNAs) in exosomes are emerging mediators of cancer-host crosstalk 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 lncRNA sequencing of 64 Medulloblastoma samples and quantified the genome wide long non coding RNAs (lncRNA) expression levels. We identified a lncRNA that is distinctly 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 (~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 expression was 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-05. GLI3 INDUCES NEOURAL 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 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.
Medulloblastomas, unlike other malignant brain tumors, are typically sensitive to radiation therapy, but the mechanisms that mediate this sensitivity are unclear. Cerebellar granule neuron progenitors (CGNPs), the cell of origin for SHH-subgroup medulloblastoma, are also highly sensitive to radiation. In early life, CGNPs proliferate in response to Sonic Hedgehog (SHH) signaling, and hyperactivation of SHH signaling in CGNPs can lead to the development of SHH-subgroup medulloblastoma. We propose that SHH activation induces radiation sensitivity in tumor cells. We have previously shown that the prosapoptotic protein BAX is required for radiation sensitivity of both SHH-driven medulloblastomas and CGNPs in mice, and that BCL-xL supplies critical regulation of BAX, preventing spontaneous tumor recurrence. However, we showed that SHH signaling increases radiation sensitivity of CGNPs by inducing the prosapoptotic protein BIM. We found that BIM expression depends on SHH activity, and that genetic depletion of Bim decreases the radiation sensitivity of CGNPs. Mechanistically, we show that SHH-induced BH3-only apoptotic proteins BCL-xL and MCL-1, where it may alter the balance of BAX and BCL-xL interactions. Consistent with our mechanistic model, human medulloblastoma patients with high BIM expression show a better prognosis. Based on these observations, we propose that SHH induction of BIM mediates the typical radiosensitivity of SHH-driven medulloblastoma. Finding ways to enhance BIM activity may open new opportunities for targeted medulloblastoma therapy.

**MBRS-10. QUESCENT SOX9-POSITIVE CELLS BEHIND MYC DRIVEN MEDULLOBLASTOMA RECURRENCE**

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Cerebellar granule neuron progenitors (CGNPs) are the cell of origin for SHH-driven medulloblastoma. CGNPs are also highly sensitive to radiation. In early life, CGNPs proliferate in response to Sonic Hedgehog (SHH) signaling, and hyperactivation of SHH signaling in CGNPs can lead to the development of SHH-subgroup medulloblastoma. We propose that SHH activation induces radiation sensitivity in tumor cells. We have previously shown that the prosapoptotic protein BAX is required for radiation sensitivity of both SHH-driven medulloblastomas and CGNPs in mice, and that BCL-xL supplies critical regulation of BAX, preventing spontaneous tumor recurrence. However, we showed that SHH signaling increases radiation sensitivity of CGNPs by inducing the prosapoptotic protein BIM. We found that BIM expression depends on SHH activity, and that genetic depletion of Bim decreases the radiation sensitivity of CGNPs. Mechanistically, we show that SHH-induced BH3-only apoptotic proteins BCL-xL and MCL-1, where it may alter the balance of BAX and BCL-xL interactions. Consistent with our mechanistic model, human medulloblastoma patients with high BIM expression show a better prognosis. Based on these observations, we propose that SHH induction of BIM mediates the typical radiosensitivity of SHH-driven medulloblastoma. Finding ways to enhance BIM activity may open new opportunities for targeted medulloblastoma therapy.