Title

DDRE-38. MAGMAS INHIBITION IN MEDULLOBLASTOMA CELL CULTURES AND PATIENT-DERIVED XENOGRAFT MODELS: POTENTIAL THERAPEUTIC IMPLICATIONS

Journal

Neuro-Oncology, 23(Supplement_6)

ISSN

1522-8517

Authors

Hoerig, Clay
Plant-Fox, Ashley
Lepe, Javier
et al.

Publication Date

2021-11-12

DOI

10.1093/neuonc/noab196.322

Peer reviewed

DDRE-35. PRE-CLINICAL ASSESSMENT OF PPRX-1701, A NANOPARTICLE FORMULATION OF 6-BROMO-ACETOXIME, FOR THE TREATMENT OF GLIOBLASTOMA

Mykola Zdioruk[1], Tomer Finkelberg[2], Michal Nowicki[1], Bin Wu[3], Yuji Takeda[3], Antonio Chiocca[4], and Sean Lawler[1]; [1]Harvey Cushing Neurooncology Laboratories, Department of Neurosurgery, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA, [2]Brigham & Women's Hospital, Boston, MA, USA, [3]Phosphorex, Hopkinton, MA, USA, [4]Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA

We previously showed that derivatives of the Chinese traditional medicine indirubin promote survival in murine glioblastoma models (Williams et al. Cancer Research 2011). However, poor drug solubility hampered further development of this approach. Here we introduce PPRX-1701, a 6'-bromoindirubin acetoxime (BiA) containing drug/polymer nanoparticle formulation which can be injected intravenously at relatively high concentrations. Mechanistically, BiA is thought to act as a broadly selective serine-threonine protein kinase inhibitor, with activity against Src family kinases, GSK-3 and JAK2. Our preliminary data show that intravenous administration of PPRX-1701 is well-tolerated and can reach intracranial murine glioblastoma as assessed by luminescent reporter assays. PPRX-1701 administration leads to improved survival in the GL261 glioblastoma mouse model (median survival 30 days (control), 47 days (treated), $p < 0.0001$). Treatment with PPRX-1701 was associated with alterations in the tumor immune microenvironment, with reduced Tregs and pro-tumor macrophages, and increased CD8+ T cells. Further preliminary mechanistic studies have shown that PPRX-1701/BiA blocks the expression multiple immunosuppressive molecules in GBM downstream of interferon-g (IFNg) including PD-L1 and indoleamine 2,3-dioxygenase 1 (IDO1) - a key enzyme in the tryptophan–kynurenine–aryl hydrocarbon receptor (Trp–Kyn–AhR) immunosuppressive pathway. BiA promoted more effective T-cell mediated tumor cell killing using patient derived glioblastoma *ex vivo* co-culture models. This data supports further development of PPRX-1701 is a candidate immunotherapeutic agent for glioblastoma treatment. Ongoing preclinical studies are investigating combination with other relevant therapies.

DDRE-36. INVESTIGATING MEDULLOBLASTOMA HETEROGENEITY AND PREDICTING COMPOUND RESPONSE

Luz Ruiz[1], and Nagi Ayad[2]; [1]University of Miami, North Miami Beach, FL, USA, [2]University of Miami, Miami, FL, USA

Medulloblastoma is the most common malignant brain tumor found in children. It is a cerebellar tumor that affects motor and cognitive processes such as coordination and movement. The standard of care is surgical removal, radiation, and chemotherapy. These treatments can be very damaging to the developing child, in that they can impair vision and walking, among other body functions. Due to this, new treatments are necessary. Treatment plans for children with medulloblastoma need to be tailored to the specific subtype that they have. Genetic studies have revealed that there are four subtypes of pediatric medulloblastoma: Group 3, Group 4, SHH, and WNT. Beyond these bulk-resolution subtypes, we hypothesize intratumor heterogeneity as a barrier to new effective treatments. I have mined single-cell RNA sequencing data to investigate cellular heterogeneity and predict compound response. I analyzed Medulloblastoma patient tumor data along with data obtained from a 10X Genomics Chromium single-cell RNA sequencing experiment performed in the laboratory from a Tg (*Neurod-Smoothened***A1*) mouse. We hypothesize that distinct cell populations within medulloblastoma should show different predicted compounds that would target them. We have ranked compound predictions to investigate whether compounds may selectively target any of these populations using transcriptional response signatures derived from the LINCS L1000 perturbagen-response dataset. We also hypothesize that Medulloblastoma tumors have distinct subtypes of cells that are preferentially sensitive to BET bromodomain, casein kinase, and ATM/ATR inhibitors. Our analysis identified ten transcriptionally distinct cell types across these medulloblastoma tumors as well as compounds predicted to target them in each transcriptional subtype. Furthermore, we identified bromodomain and casein kinase inhibitors as a potential combination therapy due to their predicted synergy at targeting all cell populations within medulloblastoma. Our studies show the importance of considering cellular heterogeneity when identifying new treatments for medulloblastoma and other brain cancers.

DDRE-37. YB-1 AS A BIOMARKER FOR DRUG RESISTANCE AND TUMOUR PROGRESSION IN MEDULLOBLASTOMA

Louisa Taylor[1], Ian Kerr[2], and Beth Coyle[1]; [1]Children's Brain Tumour Research Centre, School of Medicine, University of Nottingham Biodiscovery Institute, Nottingham, UK, [2]School of Life Sciences, University of Nottingham, NottinghamNottingham, UK

Medulloblastoma (MB) relapse is the most significant unmet clinical challenge in childhood cancer. Recently it has become evident that MBs display altered biology at relapse, indicative of the emergence and expansion of a minor, therapy resistant cancer cell population. Thus, the examination of mechanisms underlying therapy resistance is of critical importance. Y-box binding protein 1 (YB-1) is a multi-functional oncoprotein whose elevated expression and nuclear accumulation correlate with drug resistance, metastasis and disease progression in numerous cancers, although little is known about the functional role of YB-1 in MB. Genomic analysis of large-scale publicly available patient datasets revealed YB-1 expression is significantly elevated across MB molecular subgroups and high expression correlates with poor overall survival. Immunohistochemical analysis of YB-1 localisation in patient TMAs revealed significant YB-1 nuclear accumulation, suggestive of elevated YB-1 nuclear activity in these patients. Treatment of Group 3 MB cell lines (D283MED and HDMB-03) with cisplatin and subsequent analysis by nuclear/cytoplasmic fractionation and confocal microscopy revealed significantly increased nuclear and overall YB-1 expression, indicating a role for YB-1 in cellular stress response. In support of this, ChIP analysis in D283MED and HDMB-03 cell lines confirmed YB-1 interaction with multi-drug transporter gene ABCB1, while stable YB-1 knockdown resulted in significantly reduced ABCB1 expression. Likewise, knockdown of YB-1 expression in D283MED cells results in increased susceptibility of cells to vincristine, supporting a role for YB-1 in the acquisition of drug resistance in MB cell lines. Finally, whole transcriptome sequencing of YB-1-knockdown HDMB-03 and D283MED cell lines indicated YB-1 regulation of a variety of cell death, survival and metabolic pathways. We are currently using ChIP-Seq analysis to identify targetable YB-1 downstream "hits" which drive these processes. Ultimately, we aim to identify druggable targets of YB-1 allowing us to establish more effective therapeutic options for the treatment of high-risk MB.

DDRE-38. MAGMAS INHIBITION IN MEDULLOBLASTOMA CELL CULTURES AND PATIENT-DERIVED XENOGRAFT MODELS: POTENTIAL THERAPEUTIC IMPLICATIONS

Clay Hoerig[1], Ashley Plant-Fox[2], Javier Lepe[3], Christopher Douglas[3], Naomi Lomeli[4], Kaijun Di[3], Bhaskar Das[6], and Daniela Bota[4]; [1]Children's Hospital of Orange County (CHOC)/ University of California-Irvine (UCI), Orange, CA, USA, [2]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, [3]University of California Irvine, Irvine, CA, USA, [4]Department of Neurology, University of California, Irvine, Irvine, CA, USA, [6]Long Island University, Bronx, NY, USA

BACKGROUND: Brain tumors are the second most common type of pediatric cancer and are the leading cause of all cancer-related deaths in children. Medulloblastoma (MB) is the most common type of malignant pediatric brain tumor and has a five-year overall survival ranging from 40-75%, depending on the patient's age and other prognostic features. There are current anti-cancer therapies against medulloblastoma, but the treatment of recurrent disease remains a challenge. Magmas (mitochondria-associated protein involved in granulocyte-macrophage colony-stimulating factor signal transduction) overexpression has been reported in multiple types of metabolically active tissue and cancer cells, including prostate cancer, pituitary adenoma, and glioma. Limited data suggest that specific subgroups of medulloblastoma may also overexpress Magmas. This study aims to examine whether Magmas inhibition by compound "BT#9" could be beneficial for the treatment of medulloblastoma. METHODS: We studied the ability of a Magmas inhibitor (BT#9) as a therapeutic agent in stable medulloblastoma cell lines (DAOY and D283) and patient-derived primary cultures with MTT assays, migration assays, and invasion assays. RESULTS: Similar to the adult GBM studies, Magmas inhibition by BT9 had significant cytotoxic effects, causing both decreased cell proliferation and blocked cell migration in medulloblastoma cell lines DAOY and D283. IC50s determined for each during different time points demonstrated an average range of less than 3μM compared to the average range seen in adult glioblastoma cell cultures (< 10 μM). These findings suggest that the inhibition of Magmas warrants further investigation as a potential therapeutic target to optimize clinical outcomes in medulloblastoma. Our future studies will include the determination of IC50s for primary cell cultures and in vitro testing with patient-derived xenograft models.

DDRE-39. REPURPOSING CHEMOTHERAPIES AGAINST HIGH-RISK MENINGIOMAS WITH GUIDANCE BY METHYLATION PROFILES

Anh Tran[1], Wenxia Wang[1], Denise Scholtens[1], Lyndsee Zhang[2], Jenny Pokorny[1], Yufen Wang[1], Aneta Baran[1], Felix Sahm[3], Kenneth Aldape[4], David James[1], and Craig Horbinski[5]; [1]Northwestern University, Chicago, IL, USA, [2]Boardroom&Beyond, Chicago, IL, USA, [3]Dept. of Neuropathology, University Hospital Heidelberg, Heidelberg, Germany, [4]Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, USA, [5]Department of Pathology, Northwestern Feinberg School of Medicine, Chicago, IL, USA

Meningioma is the most common primary brain tumor with nearly thirty thousand new cases in the US every year. While most meningiomas are cat-