DDRE-21. THE FUNCTION OF MITOCHONDRIAL OSMR IN GLIOMA STEM CELL RESPIRATION AND GLIOBLASTOMA PATHOGENESIS

Areeza Jahani-Asl, Ahmad Sharanek; McGill, Montreal, QC, Canada

Glioblastoma contains a rare population of self-renewing brain tumor stem cells (BTSCs) which are endowed with properties to proliferate, spur the growth of new tumors, and at the same time, evade ionizing radiation (IR) and chemotherapy. However, the drivers of BTSC resistance to therapy remain largely unknown. Given its key role in oncogenesis, we hypothesized that oncokinin receptor for oncostatin M (OSMR) regulates BTSC proliferation and glioblastoma tumorigenesis. We have discovered that OSMR translocates to the mitochondria and regulates oxidative phosphorylation, independent of its role in cell proliferation. Mechanistically, OSMR is targeted to the mitochondrial matrix via the presequence translocase-associated motor complex components, mtESP70 and TIM44. OSMR interacts with NADH ubiquinone oxidoreductase 1/2 (NDUFS1/2) of complex I and promotes mitochondrial respiration. Deletion of OSMR impairs spare respiratory capacity, increases reactive oxygen species, and sensitizes BTSCs to IR-induced cell death. Importantly, suppression of OSMR improves glioblastoma response to IR and prolongs lifespan.

DDRE-22. TARGETING SERINE SYNTHESIS IN BRAIN METASTASIS

Bryce Ng0, Eugenie Kim1, Victoria Osorio-Vasquez2, Sophia Doll1, Sophia Bustraan2, Roger Liang3, Alba Luengo4, Shawn Davidson5, Ahmed Ali6, Gino Ferraro7, Grant Fischer8, Ariana Plagser9, Vinagolou Razakar4, Edward Kastenhuber4, Rosoeb Eckandari10, Sarah Bachu11, Roshan Samra12, Samuel Bakhoum9, Mattja Snuderl12, Paolo Cotzia13, John Healey14, David Sabatini15, Drew Jones16, Jean Zhao10, Min Yu17, Rakesh Jain18, Kayvan Keshari19, Michael Davies20, Matthew Vander Heiden20, Eva Hernandez-Aragon10, Matsias Mani21, Lewis Cantley22, Michael Pacold23, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 1NYU Langone Health, New York, NY, USA, 2Max Planck Institute of Biochemistry, Martinsried, Germany, 3Weill Cornell Medicine, New York, NY, USA, 4Massachusetts Institute of Technology, Cambridge, MA, USA, 5Princeton University, Princeton, NJ, USA, 6Massachusetts General Hospital, Boston, MA, USA, 7MD Anderson Cancer Center, Houston, Texas, USA, 8Whitehead Institute for Biomedical Research, Cambridge, MA, USA, 9Dana-Farber Cancer Institute, Boston, MA, USA, 10University of Southern California, Los Angeles, CA, USA

The brain environment is low in amino acids, including serine and glycine, both of which are important for tumor growth as they are precursors of proteins and nucleotide bases. How tumor cells overcome these conditions to proliferate and survive in the brain is incompletely understood. Here, we show that 3-phosphoglycerate dehydrogenase (PHGDH), which catalyzes the first and rate-limiting step of glucose-derived serine synthesis, enables brain metastasis in multiple human types and in preclinical models. Genetic suppression and small molecule inhibition of PHGDH attenuated brain metastasis, but not extra cranial tumors, and improved the overall survival of mice bearing brain metastasis. These results demonstrate that the tumor nutrient environment determines tumor cell sensitivity to loss of serine synthesis pathway activity and raise the possibility that serine synthesis inhibitors may be useful in the treatment of brain metastases.

DDRE-23. A COMPREHENSIVE CHARACTERIZATION OF THE GBM LIPIDOME REVEALS A MOLECULARLY-DERIVED SUB-GROUP WITH HIGHER SENSITIVITY TO LIPID PEROXIDATION INDUCED CELL DEATH

Danielle Morrow; Jenna Minami, Nicholas Bayley, Kevin Williams, Steven Benninger, Robert Prins, Linda Liu, Timothy Cloughesy, David Nathanson; University of California Los Angeles, Los Angeles, CA, USA

Cancers, including the universally lethal glioblastoma (GBM), have re-programmed lipid metabolism to fuel tumor growth and promote survival. However, the full extent to which lipid content is altered across molecularly heterogeneous patient tumors has yet to be fully elucidated. Additionally, the molecular alterations responsible for aberrant lipid metabolism, and the potential for identifying new therapeutic opportunities are not fully understood. To systematically investigate the GBM lipidome, we performed integrated transcriptomic, genomic and shotgun lipidomic analysis of an extensive library of glioblastomas. We comprehensively profiled across tumor microenvironments both in vivo (n=23) and in vitro (n=30). Using this comprehensive approach, we discovered two GBM sub-groups defined by their combined molecular and lipidomic profile. Triacylglycerides (TAGs) enriched in polyunsaturated fatty acids (PUFAs) were among the most significantly altered lipids between the two groups of GBM tumors. TAGs are the main components of lipid droplets, which have been shown to sequester PUFAs away from membrane phospholipids where their sensitivity to peroxidation leads to cell death. The GBM subgroup with a depletion of PUFAs TAGs showed heightened sensitivity to lipid peroxidation both under basal conditions and in response to pro-oxidant compounds in vitro. Our findings suggest a novel association between specific molecular signatures of GBM lipid metabolism and lipid peroxidation-induced cell death. This relationship may present a new therapeutic opportunity to target reprogrammed lipid metabolism in a molecularly-defined subset of GBMs.

DDRE-24. TARGETING PURINE METABOLISM TO OVERCOME GLIOBLASTOMA TUMOR RESISTANCE

Weihua Zhou1, Yangyang Yao1, Andrew Scott2, Kari Wilder-Romans1, Joseph Dressler1, Christian Werner1, Hanshi Sun1, Drew Pratt1, Peter Sajjakulnikit1, Shuang Zaho1, Mary Davis1, Barbara Nelson1, Christopher Bowenkrauk1, Li Zhang1, Francesco Gatto1, Sudharsan Srinivasan1, Neil Jairath1, Luis Correa1, Yoshie Umemura1, Angela Walker1, Maureen Kachman1, Nathan Qi2, Jann Sarkaria1, Jian Xiong2, Meredith Morgan2, Alinawaz Rehmetulla3, Maria Castro4, Pedro Lomenstein5, Stanislaw Pelc5, Theodore Costas Lyssiotis1, Daniel Wahl6, 1University of Michigan, Ann Arbor, MI, USA, 2Chalmers University of Technology, Goteborg, Sweden, 3Mayo Clinic, Rochester, MN, USA, 4First Affiliated Hospital of Nanchang, Nanchang, China

Intratumoral genomic heterogeneity in glioblastoma (GBM) is a barrier to overcoming radiation (RT) resistance. To discover genotype-independent mechanisms of RT resistance, we correlated RT resistance with the expression of approximately 700 metabolites across 23 GBM cell lines. Purine metabolites, especially those containing the base guanine, were most correlated with RT resistance. Similarly, increased abundance of tumor purines was associated with decreased survival in GBM patients treated with RT. This relationship is causal. Purine supplementation protected RT-sensitive GBMs from RT and promoted the repair of RT-induced double strand DNA breaks (DSBs). In vitro and in vivo stable isotope tracing confirmed that GBM cell lines and orthotopic patient-derived xenografts generated purines through the de novo synthetic pathway. RT treatment further increased de novo purine synthesis in GBM through signaling via the DNA damage response. Inhibition of de novo GTP synthesis with mycophenolic acid (MPA) sensitized multiple GBM cell lines and neurospheres to RT by slowing the repair of RT-induced DSBs. MPA-induced radiosensitization was GTP-dependent as it was rescued by nucleoside supplementation. Modulating pyrimidine metabolism affected neither RT resistance nor DSB repair, suggesting these GTP-specific effects are due to active signaling rather than to act as a physical substrate for DNA repair and candidate signaling molecules have been identified. These results were recapitulated in vivo with mycophenolate mofetil (MMF), the orally bioavailable FDA-approved prodrug of MPA. MMF potentiated RT efficacy, reduced tumor guanylates and slowed the repair of RT-induced DSBs across multiple models. Because de novo purine synthesis is activated by many of the oncogenic alterations that drive GBM, its inhibition is a promising genotype-independent strategy to overcome GBM RT resistance. We have now begun a clinical trial to determine whether combining MMF and RT is safe and potentially efficacious in patients with GBM.

DDRE-25. INVESTIGATING MITOCHONDRIAL SLC25A TRANSPORTERS INVOLVED IN SUPPORTING BRAIN TUMOUR METABOLISM AND SURVIVAL UNDER HYPOXIC CONDITIONS

Katherine Eales1, Alina Finch2, Victoria Wykes2, Colin Watts2, Daniel Tennant1, 1Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom, 2Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom

Advancements in prevention, detection and treatment over the last 40 years have significantly transformed cancer healthcare however there are a few cancers, such as brain tumours, which are consistently lagging behind. The most common adult brain tumour is glioma; a highly aggressive cancer that invades deep into the surrounding brain consequently making treatment challenging. The severe hypoxic nature of glioma adds further complications to therapeutic efficacy as hypoxia limits efficient drug delivery as well as increasing treatment resistance. Therapies that therefore target both the hypoxic tumour microenvironment and metabolic pathways that sustain growth have significant potential to improve patient prognosis. It is well known that cancer cellularly diverse and hypoxic brain tumours are in an altered requirement for amino acids to aid uncontrolled proliferation. Furthermore, metabolism can also be influenced by this hostile hypoxic microenvironment, leading to a more malignant phenotype. We are therefore interested in a family of mitochondrial transporters, which translocate numerous solutes across the mitochondrial membrane and are crucial for many metabolic reactions. TCGA analysis has shown that many of these amino acid carriers are upregulated in glioma. Remarkably however, around 23 of the 53 mammalian SLC25A members lack defined substrate
selectivity and so we are interested in identifying which transporters are particularly important in the metabolic adaptation to hypoxia. Using CRISPR and siRNA technologies we have identified transporters that are functionally required to maintain cell proliferation of glioma cell lines and patient tumour cells. Furthermore, using stable isotope-enriched nutrients, we have identified novel means by which glioma cell metabolism can be perturbed by inhibition of these transporters. Characterising which SLC23A transporters are important for hypoxic tumour metabolism could therefore expose a way to exploit these hypoxic areas subsequently making them more vulnerable to treatment and thus impacting patient survival.

DDRE-26. THE IMMUNO-METABOLIC ENZYME FASN PREVENTS CANCER-CELL INTRINSIC TYPE I INTERFERON RESPONSES IN GIOBLASTOMA

Mara De Martino1, Camille Daviaud1, Claire Vanpouille-Box1,2
1Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, USA, 2Sandra and Edward Meyer Cancer Center, New York, NY, USA

Glioblastoma (GBM) is a devastating primary brain cancer with a median survival of 11–15 months. Radiation therapy (RT), the standard of care for GBM patients, generates type I interferon (IFN-I) responses in patient antitumor immunity. However, these effects are sometimes mitigated by inhibitory mechanisms that are exacerbated by RT. RT can modify GBM metabolism to promote de novo lipogenesis via the fatty acid synthase (FASN). Because FASN promotes an immune-impairing IFN-I in cancer cells, we hypothesized that FASN is preventing RT-induced IFN-I responses to promote GBM survival and evade immune recognition. We first defined RT-induced metabolic changes in the GL261 murine GBM model. We observed an increase in mito-

DDRE-27. IDH MUTATED GLIOMAS PROMOTE EPILEPTOGENESIS VIA D-2-HYDROXYGLUTARATE DEPENDENT mTOR HYPERACTIVATION

Armin Mortazavi1, Islam Fayad2,5, Muzna Bachani, Tyrone Dowdy3, Joseph Steiner1, Dragomir Marc1, Chun Zhang Tang4, Miaoar Larion1, Amir Kandeh Novini3,5, Karmen Zaghari1, Joseph Lipsett2,3, Paul K. Kilburg1,4, Claire Vanpouille-Box1,2
1Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA, USA, 2Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, USA, 3Endress Health, Bethesda, MD, USA, 4Medstar Georgetown University Hospital, Washington, DC, USA, 5National Institute of Health, Bethesda, MD, USA, 6University of Maryland School of Medicine, Baltimore, MD, USA

INTRODUCTION: Epileptic seizures in patients with low-grade isocitrate dehydrogenase (IDH) mutated gliomas reach 90%, a major source of morbidity for these patients. Although there are multiple features that contribute to tumor related epileptogenesis, IDH mutations are determined to be an independent factor, although the pathogenesis remains poorly understood. We demonstrate IDH-mutated tumors promote epileptogenesis through D-2-hydroxyglutarate (D-2-HG) dependent mTOR hyperactivation. METHODS: Human glioma cell lines were treated with medium containing sodium pyruvate or without to evaluate the contribution of neuronal activity to mTOR signaling and metabolism. mTOR signaling was evaluated through western blot analysis and multiplex immunofluorescence. Neuronal activity was measured with D-2-HG, succinate, and PFI-90, a small molecule KDM inhibitor. Epileptic cortex and D-2-HG-treated neurons, have distinct metabolisms independent of neuronal activity compared to peritumoral nonepileptic cortex and control, respectively. CONCLUSION: We demonstrate IDH-mutated gliomas promote epileptogenesis through a D-2-HG dependent mTOR hyperactivation via KDM inhibition, a putative mechanism and potential therapeutic targets. Furthermore, we argue mTOR hyperactivation results in metabolic reprogramming, independent of neuronal firing, which may contribute to epileptogenesis, a heretofore unrecognized aspect of pathologic mTOR signaling in neurological diseases.

DDRE-28. MECHANISTIC AND THERAPEUTIC LINKS BETWEEN PURINE BIOSYNTHESIS AND DNA DAMAGE IN GIOBLASTOMA

Andrew Scott, Weshua Zhou, Kari Wilder-Romans, Jaine Feng, Zhe Wu, Anthony Andreen, Li Zhang, Peter Sajakulnukit, Maureen Kachman, Yoshi Umemura, Melanie Schmitt, Nathan Qi, Theodore Lawrence, Costas Lyssiotis, Daniel Wahl; University of Michigan, Ann Arbor, MI, USA

Glioblastoma (GBM) is the most common and aggressive adult brain cancer. Radiation therapy (RT) is a critical treatment modality, and development of RT resistance is the predominant cause of recurrence and mortality in GBM patients. Using cell line models as well as patient-derived xenografts and neurospheres in orthotopic brain tumor models, we have identified increased rates and dependence upon de novo purine biosynthesis as a hallmark of GBM RT resistance. More recently, we have discovered that radiation creates an acute flux through de novo purine metabolism, we hypothesize that this regulatory mechanism also exists *in vivo*. We have used advanced metabolic and metabolic tracing techniques with 13C-labeled glucose and 15N-labeled glutamine in mice bearing RT-resistant GBM patient derived orthotopic brain tumors. We found that when orthotopic GBM PD10x had elevated activity of de novo purine synthesis that increased further after RT, while normal cortex had little activity even after RT. These observations have therapeutic relevance, as targeting this metabolic pathway with the FDA-approved purine biosynthesis inhibitor mycophenolate mofetil (MMF) overcomes GBM radiation resistance in *in vivo* mouse models. The lack of de novo purine synthesis in normal cortex suggests that targeting this pathway may be tumor specific. Collectively, our data suggest that de novo synthesis of purines mediates RT resistance in GBM and that treatment of brain tumors with MMF in combination with RT may be a promising therapeutic strategy in patients.

DDRE-29. DE NOVO PYRIMIDINE SYNTHESIS IS A TARGETABLE VULNERABILITY IN IDH-MUTANT GLIOMA

Diana D. Shi1,2, Adam C. Wang1, Michael M. Levitt3, Jennifer E. Endress1,4, Min Xu5, Wentua Gao6, Januka Khanal7, Dennis Bonnal8, Harly I. Kornblum9,10, Quang-De Nguyen10, Stefan Gradl11, Andreas Sutter11, Michael Jeffers12, Andreas Janzer11, Daniel P. Cahill11, Keith L. Ligon11,12, Kali G. Abdullah13, Isaac S. gradient11,12, William G. Kaelin Jr11,12, Michael K. McGravey11
1Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA, 2Harvard Radiation Oncology Program, Boston, MA, USA, 3Children’s Medical Center Research Institute, University of Texas Southwestern Medical Center, Dallas, TX, USA, 4Ludwig Cancer Center, Boston, MA, USA, 5Harvard Medical School, Boston, MA, USA, 6Lurie Family Imaging Center, Center for Biomedical Imaging in Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 7Department of Molecular and Medical Pharmacology, University of California Los Angeles, Los Angeles, CA, USA, 8Department of Psychiatry and Behavioral Sciences, and Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA, 9Bayer AG, Berlin, Germany, 10Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA, 11Department of Neurosurgery, Translational Neuro-Oncology Laboratory, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, 12Department of Pathology, Brigham and Women’s Hospital, Boston, MA, USA, 13Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA, USA, 14Department of Neurosurgery, University of Texas Southwestern Medical Center, Dallas, TX, USA, 15Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA, 16Howard Hughes Medical Institute, Chevy Chase, MD, USA

70–90% of lower-grade gliomas and secondary glioblastomas harbor gain-of-function mutations in isocitrate dehydrogenase 1 (IDH1), causing overmetabolism of the oncometabolite (R)-2-hydroxyl glutarate (R-2HG). Although inhibitors of mutant IDH enzymes are effective in other cancers, including leukemia, they have not shown efficacy in preclinical and clinical brain tumor studies, thus underscoring the need to identify additional targets in IDH-mutant glioma. We sought to identify tumor-specific metabolic vulnerabilities induced by IDH1 mutations that could be exploited therapeutically. To un-