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 SLC25A transporters are important for glioma 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 Glioblastoma

Mara De Martino, Camille Daviaud, Claire Vanpouille-Box
Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, US,
Sandra and Edward Meyer Cancer Center, New York, NY, US

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, can generate type I interferon responses (IFN-I) to perturb and immunosuppress tumor 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 has an essential role in IFN-I signaling, 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 mitochondrial respiration, glycolysis and in lipid metabolism-related pathways in 10 gray (Gy) irradiated GL261 cells. Additionally, we found upregulation of FASN by western blot and lipid accumulation by BODIPY staining in 10 Gy-GL261 cells. RT-induced lipid accumulation was reverted when GL261 cells were incubated with a FASN inhibitor. Next, to ask whether FASN was impairing IFN-I, GL261 cells were engineered to express an inducible shRNA silencing FASN (GL261shFASN) or its non-silencing control (GL261shNS). As expected, irradiation of GL261shNS cells enhanced the secretion of IFN-β and CXCL10. This effect was more pronounced when FASN was knocked down in GL261 in combination with the presence of RT. Finally, GL261shNS and GL261shFASN cells were orthotopically implanted in mice and IFN-I signaling was blocked by anti-IFN-I receptor antibody (a-IFNAR). Mice bearing GL261shFASN tumors presented a median survival of 51 days vs. 35 days for GL261shNS tumors, a significant prolongation of survival which was completely abrogated with a-IFNAR treatment. Overall, our findings suggest that FASN-mediated lipogenesis prevents RT-induced cancer cell intrinsic IFN-I to promote GBM survival. Consequently, it is possible that FASN can act as an immunometabolic checkpoint to regulate the immune system upon metabolic cues generated by RT.

DDRE-27. IDH MUTATED GLIOMAS PROMOTE EPILEPTOGENESIS VIA D-2-HYDOXYGLUTARATE DEPENDENT MITO HYPERACTIVATION

Armin Mortazavi, Islam Fayed, Muzna Rachani, Tyrone Dowdy, Joseph Steiner, Dragomir Marc, Chun Zhang, Miosara Larjon, Kalen Underwood, Karenane Causey, Karsem Zaghdeh, Sandra and Edward Meyer Cancer Center, New York, NY, US, Medstar Georgetown University Hospital, Washington, DC, US, National Institute of Health, Bethesda, MD, US, University of Maryland School of Medicine, Baltimore, MD, US

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 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 Glioblastoma

Andrew Scott, Wenshu Zhou, Kari Wilder-Romans, Jane Feng, Zhe Wu, Anthony Andre, Li Zhang, Peter Sajakulnikut, Maureen Kachman, Yoshiy Uemura, Melanie Schmitt, Nathan Qi, Theodore Lawrence, Costas Lyssiotis, Daniel Wahl, University of Michigan, Ann Arbor, MI, US

Glioblastoma (GBM) is the most common and aggressive adult brain cancer. Radiation therapy (RT) is a critical treatment modality, and development of 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 can modify flux through de novo purine metabolism in cell line and neurosphere models of GBM. This RT-induced increase in de novo purine synthesis is dependent on signaling through the DNA damage response and appears to be an adaptive mechanism to supply purines to repair DNA-induced DNA damage. To determine whether this regulatory mechanism also exists in vivo, we have used advanced metabolomic and metabolic tracing techniques with 13C-labeled glucose and 13N-labeled glutamine in mice bearing RT-resistant GBM patient-derived orthotopic brain tumor xenografts. We find that that orthotopic GBM PDXs 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 mycophenolic acid (MMF) overcomes GBM radiation resistance in mouse models in vivo. The level 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. Shi, Adam C. Wang, Michael M. Levitt, Jennifer E. Endress, Min Xu, Wenhua Gao, Janaka Khanal, Dennis Bonaly, Harley I. Kornblum, Quang-De Nguyen, Stefan Gradl, Andreas Sutter, Michael Jeffers, Andreas Janzer, Daniel P. Cahill, Keith L. Ligon, Kali G. Abdullah, William S. Pardoll, Robert T. C. Naumov, Scott M. McBrayer, Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, US, Harwood Radiation Oncology Program, Boston, MA, US, Children’s Medical Center Research Institute at Texas Children’s Hospital, The National Institutes of Health, Bethesda, MD, US, Ludwig Cancer Center, Dallas, TX, US, Lurie Family Imaging Center, Center for Biomedical Imaging in Oncology, Dana-Farber Cancer Institute, Boston, MA, US, Department of Molecular and Medical Pharmacology, University of California Los Angeles, Los Angeles, CA, US, Department of Psychiatry and Behavioral Sciences, and Selm Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, US, Bayer AG, Berlin, Germany, Bayer HealthCare Pharmaceuticals, Whippany, NJ, US, Department of Neurosurgery, Neurosurgical Oncology Laboratory, Massachusetts General Hospital, Boston, MA, US, Department of Pathology, Brigham and Women’s Hospital, Boston, MA, US, Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA, US, Department of Neurosurgery, University of Texas Southwestern Medical Center, Dallas, TX, US, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, US, Howard Hughes Medical Institute, Chevy Chase, MD, US

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-hydroxyglutarate (R-2HG). Although inhibitors of mutant IDH enzymes are effective in other cancers, including leukemia, they have shown guarded efficacy in preclinical and clinical brain tumor studies, thus underscoring the need to identify additional, targetable vulnerabilities. In this study, we sought to identify tumor-specific metabolic vulnerabilities induced by IDH1 mutations that could be exploited therapeutically. To un-