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 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 GLIOBLASTOMA

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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 jumpstart 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 was found to impair IFN-I in antiviral immunity, we hypothesize 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-beta and CXCL10. This effect was more pronounced when FASN was abrogated in GL261 independently from 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 mice survival that 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 acts as an immuno-metabolic checkpoint capable to regulate the immune system upon metabolic cues generated by RT.

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

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INTRODUCTION: Epileptic seizures in patients with low-grade, isocitrate dehydrogenase (IDH) mutated gliomas reach 90%, a major source of morbidity for these patients. Albeit 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 and metabolic reprogramming. **METHODS:** Human epileptic and nonepileptic cortex were identified via subdural electrodes in patients with IDH-mutated gliomas (n=5). An *in vitro* rat cortical neuronal model on microelectrode arrays were utilized to investigate the role of D-2-HG on neuronal excitability. mTOR and lysine demethylase (KDM) modulators were applied to elucidate the epileptogenic mechanism. Tetrodotoxin was utilized to evaluate the contribution of neuronal activity to mTOR signaling and metabolism. mTOR signaling was evaluated through western blot analysis and multiplex immunofluorescence. Metabolic function were analyzed via Seahorse assays and metabolomic analysis. **RESULTS:** D-2-HG increased normalized bursting rate in the neuronal cultures ($p<0.0001$). Inhibition of mTOR with rapamycin corrected bursting levels to control levels. Furthermore, D-2-HG induced mTOR hyperactivation, independent of bursting activity, which correlated with upregulation of mTOR signaling in human epileptic tissue. KDM inhibition resulted in mTOR hyperactivation and neuronal hyperexcitability, which we demonstrated 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 GLIOBLASTOMA

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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 treatment acutely stimulates flux through *de novo* purine synthesis 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 thus appears to be an adaptive mechanism to supply purines to repair radiation-induced DNA damage. To determine whether this regulatory mechanism also exists *in vivo*, we have used advanced metabolomic and metabolic tracing techniques with ^{13}C-labeled glucose and ^{15}N-labeled glutamine in mice bearing RT-resistant GBM patient-derived orthotopic brain tumors. We found 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 mycophenolate mofetil (MMF) overcomes GBM radiation resistance in mouse models *in vivo*. 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

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70–90% of lower-grade gliomas and secondary glioblastomas harbor gain-of-function mutations in isocitrate dehydrogenase 1 (*IDH1*), causing overproduction 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 therapeutic targets in *IDH* mutant glioma. We sought to identify tumor-specific metabolic vulnerabilities induced by *IDH1* mutations that could be exploited therapeutically. To un-