glycolytic profile that are thought to be responsible of the resistance of GBM to treatments. Metabolic reprogramming allows tumor cells to survive in unsupported microenvironments. Manipulating tumor metabolism to counteract GBM resistance arises as a powerful approach with minimal effects in normal counterparts. At pharmacological concentrations, melatonin displays oncostatic properties. This is thought to be due to an increase in mitochondrial oxidative phosphorylation through the effects of melatonin in mitochondria, which organelles are in metabolic stress. We hypothesized that melatonin could alter B1C metabolism, by inducing an anti-Warburg effect and as consequence, melatonin will decrease the viability of GBM cells and tumor growth. We found that treatment of GBM cell lines with 3mM melatonin significantly altered tumor cell metabolism. We observed that melatonin downregulated the lactate symmetry MCT4 (p<0.002), inducing a significant intracellular accumulation of lactate (p<0.002) while decreasing it in the extracellular media (p<0.001). This was followed by a decrease in the internal pH (p<0.002). These effects were compensated by an increase in the oxygen consumption rate (OCR) followed by decay that led to an increase in ROS production (p<0.001). All these changes result in a depletion of cellular ATP (p<0.001) and eventually drove to a decrease in the proliferation (p<0.001) and cell death (p<0.001). When applied in vivo we observed a significant reduction in the tumor growth (p<0.001), volume (p<0.002) and weight (p<0.002), as well as a drop in the proliferation marker ki67 (p<0.001) and a fibrosis increase in treated tumors. These results position melatonin as a strong therapeutic candidate for GBM therapy.

**DDRE-34. TARGETING RESISTANCE IN MEDULLOBLASTOMA**

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Medulloblastoma is the most commonly diagnosed pediatric brain tumor. Although therapeutic advances have improved survival from this cancer, they result in devastating sequelae and, additionally, have proven inadequate in controlling local tumor and recurrence when they remain. Therapeutic therapies are urgently needed to improve outcomes in medulloblastoma. Medulloblastoma development is driven by deregulation of normal cerebellar proliferation. Mutations in the sonic hedgehog (Shh) pathway are found in ~30% of these tumors and responsible for their aggressive growth. The poor outcomes in Shh-driven medulloblastoma have prompted the evaluation of Shh-targeting agents in their treatment – with limited success likely attributable in part to the upregulation of alternate survival pathways (e.g. Ras/MAPK and HIF-1α). These alternate mechanisms stimulate glycolysis, in part by increasing the activity of the 6-phosphofructo-2-kinase/fructose-2,6 bisphosphatases (PFKFB1-4) to produce fructose-2,6-bisphosphate (F26BP), a potent activator of the rate-limiting glycolytic enzyme, 6-phosphofructo-1-kinase. In recent studies, we have determined that the PFKFB4 enzyme is highly expressed in patient-derived Shh medulloblastomas. We have found that hypoxia, through HIF-1α, strongly induced PFKFB4 expression in Shh-driven medulloblastoma cells and that silencing PFKFB4 suppressed F26BP, glycolysis and proliferation in normoxia and, more markedly, in hypoxia, indicating that PFKFB4 may be required for growth under hypoxia. We found that simultaneously silencing PFKFB4 and Shh pathway effectors significantly reduced cell survival and that co-targeting PFKFB4 (with a novel inhibitor) and Shh effectors synergistically decreased cell viability. In order to further emphasize the metabolic heterogeneity of glioblastoma (GBM), we have now subjected Shh medulloblastoma cells to prolonged Shh inhibitor exposure and found that these cells exhibit increased proliferation, glycolysis and PFKFB4. Studies are underway to delineate their metabolic alterations. Taken together, our data indicate that targeting PFKFB4 may be a valid therapeutic option in aggressive, treatment-resistant medulloblastoma and strongly support the further examination of PFKFB4 inhibitors in these tumors.

**EPIGENOME, TRANSCRIPTOME, METABOLOME AND MODELING**

**ETTM-01. CANCER STEM CELL ENRICHMENT AND METABOLIC SUBSTATE ADAPTABILITY ARE DRIVEN BY HYDROGEN SULFIDE SUPPRESSION IN GLIOBLASTOMA**

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Glioblastoma (GBM) remains among the deadliest of human malignancies. From the cancer stem cells (CSC) phenotype supported by the LCN2/SCL22A17 pathway is a major challenge to disease management and durable treatment response. The extrinsic, environmental, and lifestyle factors that result in CSC enrich-

**ETTM-02. PRECLINICAL MODELS REVEAL BRAIN-MICROENVIRONMENT SPECIFIC METABOLIC DEPENDENCIES IN GLIOBLASTOMA**

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Metabolic reprogramming is a hallmark of cancer, and malignant cells must acquire metabolic adaptations in response to a multitude of intrinsic and extrinsic factors to fuel neoplasic progression. Mutations or changes in metabolic gene expression can impose nutrient dependencies in tumors, and even in the absence of metabolic defects, cancer cells can become auxotrophic for particular nutrients or metabolic byproducts generated by other cells in the tumor microenvironment (TME). Conventional cell lines do not recapitulate the metabolic heterogeneity of glioblastoma (GBM), while primary cultured cells do not account for the influences of the microenvironment and the blood brain barrier on tumor biology. Additionally, these systems are under strong selective pressure divergent from that in vivo, leading to reduced heterogeneity between cultured tumor cells. Here, we describe a biobank of direct-from-patient derived orthotopic xenografts (GliomaPDOX) and gliomaspheres that reveal a subset of gliomas that, while able to form in vivo, cannot survive in vitro. RNA sequencing of tumors that can form both in vivo and in vitro (termed “TME-Indifferent”) compared to that of tumors that can only form in vivo (termed “TME-Dependent”) revealed transcriptional changes associated with altered nutrient availability, emphasizing the unique metabolic programs impacted by the tumor microenvironment. Furthermore, TME-dependent tumors lack metabolic signatures associated with nutrient biosynthesis, thus indicating a potential dependence of these tumors on scavenging specific nutrients from the extracellular milieu. Collectively, these data reveal that gliomaspheres and orthotopic xenografts represent GBM by restricting metabolic adaptability, while its loss triggers CSC enrichment and disease acceleration. Interventions augmenting HIF bioavailability concurrent with GBM standard of care may improve outcomes for GBM patients.