glycolytic profile that are thought to be responsible of the resistance of GBM to treatments. Metabolic reprogramming allows tumor cells to survive in unsupportive microenvironments. Manipulating tumor metabolism to counterract 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, they organelle that generates ATP in the process of aerobic respiration. 

We have found that treatment of GBM cell lines with 3mM melatonin significantly altered tumor cell metabolism. We observed that melatonin downregulated the lactate synthase 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 intracellular 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.

**ETMM-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 neoplastic 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 autotrophic 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 dependency of these tumors on scavenging specific nutrients from the extracellular milieu. Collectively, these data emphasize the metabolic heterogeneity within glioblastoma and reveal a subset of gliomas that lack metabolic plasticity, indicating a potential brain-microenvironment specific metabolic dependency that can be targeted for therapy.